Symposium on Peripheral Vascular Disease
(Concluded)

Minnesota Medicine

Contents for May

SCIENTIFIC ARTICLES

ORIGINAL CONTRIBUTIONS

MEDICAL PROGRESS

CASE PRESENTATIONS

Owner and Publisher

MINNESOTA STATE MEDICAL ASSOCIATION
496 Lowry Medical Arts Building
St. Paul 2, Minnesota

Publishing and Finance Committee

E. M. HAMMES, M.D.
Chairman, Saint Paul
F. M. OWENS, JR., M.D.
Saint Paul
T. A. PEPPARD, M.D.
Minneapolis
HENRY ULRICH, M.D.
Minneapolis

Business Manager

R. R. ROSELL
496 Lowry Medical Arts Building
St. Paul 2, Minnesota

Authors

Manuscripts should be addressed to Arthur H. Wells, M.D., Editor, 915 East First Duluth 5, Minnesota. Telephone RA 7-6636 or JA 5-2319. Original papers prepar publication solely in MINNESOTA MEDICINE will be considered by the Board of providing they fulfill the following editorial standards. Manuscripts should be double spaced on white paper with at least 1-inch margins. The original (not a copy) is requested. The title on the first page should be under six words if poss divided into two parts. The author should give his highest degree, his institutional or his relationship to a hospital or medical organization which he may be add Pages should be numbered consecutively and the author's last name should appear top of each page after the first page.

Bibliographical references should appear on a separate sheet entitled "Bibliography." should appear and be numbered consecutively in the order in which they first in the text (not alphabetically). Citations in the text require reference numbers author's or authors' names are not used or if there is more than one reference same author or group of authors. All references to author should appear in the Biblio and no references should be included which are not in the text. The style and punctuation used in the J.A.M.A. references are requested. Journal references sho include: *Author's last name, initial., initial.: title of paper. Abbreviated name of j volume number: page, year.* Book references should give author, title, edition numbe publisher and year.

Illustrations (photographs, tables and graphs) should be submitted separately a combined in the text. There should be a separate sheet entitled "Illustrations" contains the various types of illustrations listed separately and numbered in the

Symposium on Peripheral Vascular Disease
(Concluded)

Minnesota Medicine

Contents for May

SCIENTIFIC ARTICLES

ORIGINAL CONTRIBUTIONS

MEDICAL PROGRESS

CASE PRESENTATIONS

Owner and Publisher

MINNESOTA STATE MEDICAL ASSOCIATION
496 Lowry Medical Arts Building
St. Paul 2, Minnesota

Publishing and Finance Committee

E. M. HAMMES, M.D.
Chairman, Saint Paul
F. M. OWENS, JR., M.D.
Saint Paul
T. A. PEPPARD, M.D.
Minneapolis
HENRY ULRICH, M.D.
Minneapolis

Business Manager

R. R. ROSELL
496 Lowry Medical Arts Building
St. Paul 2, Minnesota

Authors

Manuscripts should be addressed to Arthur H. Wells, M.D., Editor, 915 East First Duluth 5, Minnesota. Telephone RA 7-6636 or JA 5-2319. Original papers prepar publication solely in MINNESOTA MEDICINE will be considered by the Board of providing they fulfill the following editorial standards. Manuscripts should be double spaced on white paper with at least 1-inch margins. The original (not a copy) is requested. The title on the first page should be under six words if poss divided into two parts. The author should give his highest degree, his institutional or his relationship to a hospital or medical organization which he may be add Pages should be numbered consecutively and the author's last name should appear top of each page after the first page.

Bibliographical references should appear on a separate sheet entitled "Bibliography." should appear and be numbered consecutively in the order in which they first in the text (not alphabetically). Citations in the text require reference numbers author's or authors' names are not used or if there is more than one reference same author or group of authors. All references to author should appear in the Biblio and no references should be included which are not in the text. The style and punctuation used in the J.A.M.A. references are requested. Journal references sho include: *Author's last name, initial., initial.: title of paper. Abbreviated name of j volume number: page, year.* Book references should give author, title, edition numbe publisher and year.

Illustrations (photographs, tables and graphs) should be submitted separately a combined in the text. There should be a separate sheet entitled "Illustrations" contains the various types of illustrations listed separately and numbered in the

Volume 41
Number 5

MISCELLANEOUS ARTICLES

ORMATION

ich they appear in the text. All photographs must be in black and white, clear ontrasting, and on glossy prints. Instructions for combining photographs are able. Any number of illustrations over 4 are charged to the author. Combinations otographs up to one-half page (6 x 4⅜ inches) count as 1 illustration.

ers and Reviewers

e right is reserved to reject material submitted for reading or advertising columns. iews expressed in this journal do not necessarily represent those of the Minnesota Medical Association or any of its constituents.

rtisers and Subscribers

ssified advertising—15 cents a word; minimum charge $3.00; key number, 25c onal. Remittance should accompany order. Display advertising rates on request.

ual Subscription—$5.00. Single Copies—$0.50. Foreign and Canadian—$5.50.

mmunications concerning advertising and subscriptions should be addressed to esota Medicine, 2642 University Avenue, Saint Paul 14, Minnesota. Telephone ay 6-2641.

right and Post Office Entry

ered at the Post Office in Saint Paul as second class matter. Accepted for mailing at pecial rate of postage provided for in Section 1103, Act of October 3, 1917, rized July 13, 1918.

Original Contributions

Clinical Aspects of Pheochromocytoma

WALTER F. KVALE, M.D.
Rochester, Minnesota

THE DIAGNOSIS of functioning pheochromocytoma is becoming less difficult as experience increases. Careful appraisal of the history, close scrutiny of the patient's age, weight and body build, and study of certain laboratory data often afford a clue at the first or second interview.

Since the first pharmacologic test for pheochromocytoma was introduced, my associates and I have had the opportunity of studying carefully fifty-seven patients who had pheochromocytomas. It is the purpose of this paper to present pertinent data on the diagnostic aspects and the results in fifty of these patients, to demonstrate that the diagnosis can be made if the possibility of this condition is kept in mind, to summarize indications for performing pharmacologic and other tests for pheochromocytoma, and to show that the transabdominal approach should be used and that cure is usually but not always possible.

Classification

The grouping of patients with hypertension caused by pheochromocytoma in those who have paroxysmal hypertension and those who have sustained hypertension is largely arbitrary. In general, those patients whose tumors secrete epinephrine and norepinephrine intermittently have paroxysmal hypertension, whereas those whose tumors secrete pressor substances continuously have persistent hypertension. However, the latter group also may have attacks during which the blood pressure is even higher than usual.

A total of twenty-six patients were classed as having paroxysmal hypertension. All twenty-six complained of episodes associated with pronounced increase in blood pressure. Between these attacks, the blood pressure was normal. The remaining twenty-four patients were considered to have persistent hypertension. Although their blood pressure was increased almost continuously, in some it would be normal or approach normal at times. The periods of increased blood pressure sometimes were associated with "spells," although not all patients had them.

Symptoms

Paroxysmal Hypertension.—As already noted, all the patients who had paroxysmal hypertension complained of spells, or attacks. Headache of varying intensity, but usually extremely severe, was the commonest symptom and was present in all except one patient. Sweating and palpitation were the next commonest symptoms. Also present were tachycardia, great anxiety, nervousness, pallor or flushing of the face, nausea and vomiting, pain in the thorax and abdomen, pain and numbness in the legs, and tingling and coldness of the hands and feet. In any patient, one or more of these symptoms could be lacking.

The duration of the illness varied from six weeks to ten years, the usual time being two to five years. The length of the history had no bearing on the secondary vascular damage that the intermittent discharge of the pressor amines might have produced. One woman who had been having bouts of excruciating headaches as frequently as several times a week for ten years had normal ocular fundi and a normal vascular system. On the other hand, a thirty-eight-year-old man who had had symptoms for only eight months had both coronary occlusion and thrombosis of the basilar artery before the diagnosis could be made.

The frequency of the attacks varied from as often as ten to twenty-five a day to once a day or even to only once every two to three months. They usually lasted only ten to fifteen minutes, but some persisted only a few seconds and others

From the Section of Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

Presented at the Symposium on Peripheral Vascular Disease co-sponsored by the Minnesota Heart Association and the Mayo Foundation, Rochester, Minnesota, September 25, 1957.

for several hours or days. Weakness and exhaustion commonly followed an attack. The usual story was that the attacks increased in frequency but not in severity. Between attacks, the patients were generally in good health.

Persistent Hypertension.—The twenty-four patients classed as having persistent hypertension had more or less continuous hypertension. However, ten complained of attacks similar to those experienced by patients who had only paroxysmal hypertension. During these attacks, the blood pressure increased to even higher levels. The usual picture was that of increasingly severe headaches, excessive perspiration, nervousness, palpitation and loss of weight. All twenty-four patients with persistent hypertension were thin, although two patients seen recently were slightly obese. If the condition has been unrecognized, changes due to secondary vascular damage, such as loss of vision, coronary occlusion, cerebrovascular thrombosis and congestive heart failure, may be responsible for the chief complaints.

Symptoms had been present for three weeks to sixteen years, the average being three to four years. The duration of the symptoms closely paralleled the duration of the hypertension, although hypertension in one case was not discovered for five years after the onset of symptoms.

Findings at Examination

Paroxysmal Hypertension.—The average age of patients with paroxysmal hypertension was forty-four years, ranging from twenty-six to fifty-nine. They tended to be older than those who had persistent hypertension. Only one patient was in the third decade of life; most (ten) were between thirty and forty years of age.

The height ranged from 62 to 72 inches (157 to 182 cm.). The average height of twenty-one patients was 65 inches (165 cm.). The patients also tended to be thin, ranging in weight from 106 to 192 pounds (48 to 87 kg.), with an average of 134 pounds (61 kg.). The patient who weighed 192 pounds was 70 inches (178 cm.) in height.

The level of blood sugar during a period of fasting was determined in twenty-five of these twenty-six patients under normotensive conditions; values greater than normal were found in eleven. The basal metabolic rate also was determined in twenty-five of the twenty-six patients. Values were more than +20 per cent in five, the highest rate being +33 per cent; they were between +11 and +20 per cent in five patients and were normal in fifteen. The basal metabolic rate was of aid in making the diagnosis of pheochromocytoma in only six cases. In general, the basal metabolic rate and level of blood sugar were not of material help in making the diagnosis in this group.

Excretory urograms were made in all cases. They gave evidence of a mass above one of the kidneys or displacement of the kidney in seven of the twenty-six cases.

Aortograms, perirenal injections of air and presacral injections of oxygen have not been used by us because localization is not considered necessary before operation. These procedures also entail an unnecessary risk to the patient.

Persistent Hypertension.—The average age of the twenty-four patients was thirty-five and six-tenths years, ranging from twelve to sixty-seven years. However, sixteen of the twenty-four were less than forty years of age and only two were more than sixty, being sixty-seven and sixty-five years old, respectively.

The average height of twenty of these twenty-four patients was 65 inches (165 cm.). The average weight of twenty-three of them was 122 pounds (55 kg.). Only five of the patients weighed more than 134 pounds (61 kg.). The two heaviest, weighing 169 and 160 pounds (77 and 73 kg.), were both 70 inches (178 cm.) tall. Eleven weighed 113 pounds (51 kg.) or less. The range in weight was 90 to 169 pounds (41 to 77 kg.). These patients generally were much thinner than those who had paroxysmal hypertension.

The basal metabolic rate was determined in twenty-one of the twenty-four patients. It ranged from +8 to +101 per cent and was more than +20 per cent in sixteen. Hypermetabolism without hyperthyroidism was of significant help in making the diagnosis in eighteen of these patients. In only three patients was the basal metabolic rate less than +10 per cent.

The level of blood sugar was determined in seventeen of the twenty-four patients; it ranged from 107 to 256 mg. per 100 ml., and in ten patients it was 120 mg. or more.

The excretory urogram was of help in localizing the tumor in four of the twenty-four patients. In one instance, however, the urogram indicated that the tumor might be on the right, whereas actually it was found on the left.

Findings at Operation

Paroxysmal Hypertension.—At the time of operation, nineteen tumors were removed from the right adrenal and five from the left. The tumors were bilateral in the two remaining patients. In one case of bilateral lesions, two tumors were removed from the right adrenal and one from the left; in the other case of bilateral tumors, the mass on the right was removed but the one on the left was not.

Seven of these twenty-six patients had gallstones. These were found before, at the time of, or after removal of the pheochromocytoma. The large percentage of gallstones in this series of cases suggests more than coincidence.

Persistent Hypertension.—There were thirteen tumors in the right adrenal, thirteen in the left and a total of six extra-adrenal tumors, three of which were inoperable metastatic lesions at the time of operation. One of the remaining extra-adrenal tumors was retroperitoneal on the left side, and one was situated behind the structures at the hilus of the liver. In one patient who had multiple tumors, three lesions arose from the right adrenal, one arose from the left adrenal and an additional tumor was found behind the right lobe of the liver. Thus, a total of thirty-two tumors were found in these twenty-four patients. None of them had gallstones. In one other case, two more tumors were found along the aortic chain at re-operation.

Type of Tumor and Results

Paroxysmal Hypertension.—In the twenty-six patients who had paroxysmal hypertension, all tumors except one were benign, and this one was considered benign until it recurred. Re-operation disclosed a fixed mass in the right adrenal region with metastasis to the liver.

Follow-up information was obtained on twenty-four of the twenty-six patients. All except two were living at the last report. One of the two who died had active pulmonary tuberculosis at the time of operation and subsequently died of this disease; the other died from causes other than pheochromocytoma ten years after the tumor was removed. Five patients have had further difficulty; one had residual effects from a cerebral infarct, one had metastasis found at re-operation and treated roentgenologically, and the other three had only minor difficulties. The remaining seventeen patients were living and well at last report.

Persistent Hypertension.—The lesions in seventeen of these twenty-four patients were benign; one patient had a malignant tumor and three had tumors that were apparently benign on pathologic examination but metastasis occurred later. Inoperable fixed pheochromocytomas were found at operation in the remaining three patients, all of whom died soon afterward of metastasis.

Thus, seven of these twenty-four patients with persistent hypertension had potentially fatal pheochromocytomas, and six of these have died from the effects of malignancy. The seventh has had recurrent tumors removed but was still living, although he had metastasis. One other patient died, presumably from metastasis from a carcinoma of the pancreas, and still another one died after sympathectomy.

The remaining fifteen patients were living and well at last report, although one had residual homonymous hemianopsia that developed after operation. Three have noted residual mild hypertension. In all patients in whom the changes in the retinal vessels were those of hypertension Group 3 or 4, the changes have reverted to those of hypertension Group 1 or 2.

Surgical Aspects

Frequent determination of blood pressure and its proper control are among the most important procedures during operation on a patient who has pheochromocytoma. Characteristically, the blood pressure fluctuates widely during removal of a pheochromocytoma. It usually increases sharply with induction of anesthesia. This increase commonly continues as the incision is made and becomes more pronounced as the tumor is palpated and mobilized. After the tumor is removed, the blood pressure decreases sharply to levels typical of shock. This drop is usually most pronounced in patients who had persistent hypertension before operation. Actually, if this decrease does not occur at this time, the presence of an additional tumor that has not been removed should be suspected. Because of these wide fluctuations in blood pressure, which may have serious results if not properly treated, it is essential to have depressor as well as pressor agents readily available during operation.

It is our practice always to insert a needle in a vein and start a slow infusion of a 5 per cent solution of dextrose before induction of anesthesia. Phentolamine (regitine) hydrochloride in doses of 5 mg. is used as the depressor agent, and levarterenol (levophed) bitartrate in doses of 4 mg. is used as the pressor agent. When the blood pressure increases with induction of anesthesia, it may be advisable to inject regitine. This is always true as the tumor is palpated and mobilized. After removal of the tumor, levophed is employed. If the blood pressure does not decrease after removal of a tumor, further confirmation of another tumor may be obtained by administration of regitine, which, under these circumstances, may be expected to cause a definite decrease in blood pressure.

Various surgical approaches have been used in operations for pheochromocytoma. It is our belief that a transverse upper abdominal incision is the approach of choice. This exposure permits simultaneous exploration of both adrenal glands through a single incision and also affords opportunity for general abdominal exploration. It obviates the need for examinations for localization of a tumor in one adrenal gland, such as perirenal or presacral injection of air or aortography, since both adrenal glands are routinely palpated and inspected at operation. Exploration of the abdomen and opposite adrenal gland from a posterolumbar incision on one side has not been satisfactory in our experience.

Although it is true that pheochromocytoma usually is a single benign tumor in one adrenal gland, these tumors may be multiple on one side or bilateral, they may be malignant, and they may be located wherever chromaffin tissue is found. Because of the possibility of multiple, bilateral or ectopically located tumors, both adrenal glands should be explored in every patient and, in addition, general abdominal exploration should be done. Particular attention is given to the region of the great vessels in the abdomen and the base of the mesentery of the small intestine. Fortunately, almost every patient who has a pheochromocytoma is thin, which facilitates the abdominal approach.

Appropriate postoperative care after removal of a pheochromocytoma is extremely important. This is likely to be especially true if the patient has had sustained hypertension before operation. The main concern during the postoperative period is maintenance of adequate blood pressure. The pronounced hypotension that becomes evident on removal of a functioning pheochromocytoma may persist for hours or several days after operation unless proper supportive measures are employed. These patients should be kept under constant observation, with frequent determinations of blood pressure until reasonable levels of blood pressure persist without support. It is our practice during this period of pronounced hypotension to use a slow but continuous drip of 1000 ml. of a 5 per cent solution of dextrose to which 4 mg. of levophed has been added.

Indications for Tests for Pheochromocytoma

One of the problems in diagnosis is to ascertain under what conditions the presence of a pheochromocytoma should be suspected and when laboratory tests for pheochromocytoma should be ordered. Our data indicate that patients of the following types should be scrutinized with the possibility of pheochromocytoma in mind; if other diagnostic possibilities are ruled out, it might be wise to perform pharmacologic tests for pheochromocytoma on them:

1. Any patient who complains of "spells" associated with headache, perspiration, thoracic and abdominal pain, nervousness and vasomotor phenomena should have a pharmacologic test.

2. Thin patients with histories of fluctuating hypertension but whose blood pressure is within normal limits on examination probably should have a histamine test. All other thin patients with hypertension should undergo the appropriate test.

3. All young persons with hypertension should be tested. Only three of our twenty-four patients with persistently functioning pheochromocytomas were more than fifty years old, and sixteen were less than forty years of age. If results of regitine tests in such persons are negative or equivocal, the procedure should be repeated, other tests should be performed, or the concentration of pressor amines should be determined.

4. All persons who have hypermetabolism without hyperthyroidism should be investigated. In sixteen of our twenty-four patients with persistently functioning pheochromocytomas, the basal metabolic rate was more than +20 per cent and hyperthyroidism and other causes of hypermetabolism had been excluded.

5. All persons with a short history of hypertension should be considered for tests. Hyper-

tension had been known for only three weeks in one of our patients, an eighteen-year-old girl. In two patients, hypertension was discovered on examination at the clinic. However, the symptoms of hypertension ordinarily closely approximate the known duration of the hypertension.

6. All patients who have severe hypertension Group 2, 3 or 4 who are not included in the foregoing categories should undergo tests. Fifteen of the twenty-four patients with persistently functioning pheochromocytomas had ocular evidence of hypertension Group 3 or 4.

7. Patients who respond in a paradoxic fashion to the ganglion-blocking agents should be considered for pharmacologic tests. In one of our patients, severe increase in blood pressure occurred after the initial hypotensive reaction from subcutaneously injected hexamethonium.

8. When a patient responds unsatisfactorily to anesthesia and the blood pressure increases, the administration of the anesthetic agent should be stopped immediately, for this reaction could indicate a pheochromocytoma.

Summary and Conclusions

A study has been made at the Mayo Clinic on fifty patients who had surgically proved pheochromocytomas. These tumors, although rare, can be detected in many instances by careful appraisal of the history, close scrutiny of the patient's age and weight, and use of either the histamine or phentolamine (regitine) test or both. If any question remains, determination of the pressor amines in the blood during the time of the highest blood pressure is needed. Pheochromocytomas appear to be peculiar to thin people, especially those who have persistent hypertension. Those patients with hypertension who are young, are thin, have lost weight and have hypermetabolism without hyperthyroidism should have the pharmacologic tests for this lesion.

The tumors are usually benign. Their removal may prevent secondary vascular changes, such as visual impairment, coronary occlusion, congestive heart failure and cerebrovascular accidents, and may be lifesaving. The tumors may be malignant and some that at first are considered benign later may become malignant and metastasize. They may recur. Therefore, the diagnosis and removal of pheochromocytomas do not always insure a promising outcome. The pheochromocytomas in eight of these fifty cases (16 per cent) were malignant or have become malignant; the largest number of malignant lesions occurred in persistent hypertension. More than a coincidental relationship apparently exists between gallstones and pheochromocytoma.

Pheochromocytomas may be located anywhere in the abdominal cavity. It is not necessary to localize them preoperatively, since an anterior abdominal approach allows free exploration. After removal of a pheochromocytoma, patients should be examined frequently to be sure that recurrence has not developed nor metastasis occurred. If either is present, further operative or roentgenologic treatment may prolong the life of the patient.

EMERGENCY IDENTIFICATION CARD FOR PATIENTS ON ANTICOAGULANT THERAPY

An "emergency" identification card for the protection of patients on long-term anticoagulant therapy is now available to physicians from the American Heart Association and its affiliates.

The card, designed as a wallet insert, was developed as a result of requests from physicians seeking to protect their patients on anticoagulants in case of accident, dental surgery or other treatment that may induce bleeding. It points out that the bearer "is being treated with anticoagulants which slow down clotting of the blood." In case of emergency—bleeding, injury or illness—the card advises that a doctor be called, since the patient may require an antidote.

The card contains space for the name, address and phone number of the individual's physician. There is also space to indicate the kind of anticoagulant prescribed and the patient's blood type. The card was designed with the approval of the Committee on Prothrombin Determinations of the American Heart Association.

In addition to making the anticoagulant identification card available to physicians, the Heart Association also is calling it to the attention of dentists, hospital emergency room personnel, nurses, police and others who most commonly handle emergencies.

Physicians may obtain samples of the identification card from their local Heart Association or from the American Heart Association at 44 East 23rd Street, New York City.

Pressor Amines in Pheochromocytoma

WILLIAM M. MANGER, M.D.
Rochester, Minnesota

THE FLUOROMETRIC method of Weil-Malherbe and Bone,[1] with some modifications,[2] was used for the quantitation of epinephrine and norepinephrine in the plasma of patients with essential hypertension and those with pheochromocytomas.

In healthy men and women, the highest concentration of epinephrine-like substance per liter of plasma was 3.6 micrograms. The concentration of epinephrine-like substance in more than 90 per cent of an equally large number of patients with essential hypertension was less than 3.6 micrograms per liter of plasma; however, several of these patients occasionally had concentrations of 4 to 5 micrograms.

In twenty-three patients with pheochromocytomas, all but one of those who had sustained hypertension and two of those who had paroxysmal hypertension had concentrations of epinephrine-like substance greater than 3.5 micrograms per liter of plasma; values for the sum of epinephrine and norepinephrine when hypertension was sustained or when blood was drawn during a paroxysmal episode of hypertension were more than 8.8 micrograms in these same patients. Further studies on the three patients with pheochromocytomas and normal plasma concentrations of pressor amines showed that the amount of pressor amines increased above normal in the patient with persistent hypertension and in one of the two patients with paroxysmal hypertension after a provocative histamine test. Unfortunately, the effect of histamine was not studied in the third patient, but the plasma concentration of pressor amines was abnormally increased during anesthesia in this instance. Administration of a general anesthetic agent often simulates a provocative test in patients who have pheochromocytoma.

Patients with renal insufficiency should be carefully evaluated, since this condition may be associated with retention of fluorescent substances other than epinephrine and norepinephrine that give falsely high values for plasma pressor amines. Some patients with brain tumors or lymphomas have concentrations of plasma pressor amines that are above the range of normal. It is uncertain whether the substances measured as pressor amines in patients who have lymphomas are epinephrine or norepinephrine or both or some other substances. One patient with acute pancreatitis had greatly increased values for epinephrine-like substance in the plasma; however, the presence of hyperbilirubinemia in this patient made it uncertain whether an actual increase in plasma pressor amines was present. My associates and I have found that bile pigments or hemolysis will interfere with the fluorometric quantitation of epinephrine and norepinephrine in plasma by producing sufficient fluorescence to indicate erroneously increased concentrations of pressor amines.

We recently observed a patient with persistent hypertension who for many years had been using "asthma-nefrin," a solution of epinephrine hydrochloride, in a nebulizer for treatment of recurrent attacks of asthma. Mild azotemia also was present. Despite the fact that asthma-nefrin had not been used for about forty hours, the concentration of epinephrine-like substance was 5.1 micrograms per liter of plasma and results of the phentolamine (regitine) test were equivocal. The patient subsequently used nebulized asthma-nefrin during an acute attack of asthma; forty-one hours later, the concentration of epinephrine-like substance averaged 12.2 micrograms and results of the regitine test again were equivocal. Because a diagnosis of pheochromocytoma could not be excluded, exploratory laparotomy was performed but a tumor

(Continued on Page 321)

Abstract of paper presented at the Symposium on Peripheral Vascular Disease co-sponsored by the Minnesota Heart Association and the Mayo Foundation, Rochester, Minnesota, September 25, 1957.

Dr. Manger is a Fellow in Medicine, Mayo Foundation, Rochester, Minnesota. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

Laboratory Diagnosis of Pheochromocytoma

GRACE M. ROTH, Ph.D.
Rochester, Minnesota

IN OTHER presentations in this symposium, Dr. Kvale and Dr. Manger have discussed certain aspects of the diagnosis of pheochromocytoma. Despite the excellent method described by Dr. Manger, which is sensitive and extremely useful, the diagnosis of pheochromocytoma is still a challenge and, if anything, is becoming more difficult to make. Some additional laboratory methods for this diagnosis, with their merits and defects, also should be considered.

Pharmacologic Tests

The patient who has a pheochromocytoma will have either paroxysmal or sustained hypertension. When the hypertension is paroxysmal, the most effective drug in my experience for the diagnosis of pheochromocytoma is histamine, which stimulates discharge of pressor substances from the tumor and produces attacks similar to those occurring spontaneously. Likewise, if the patient has mild hypertension and a history of paroxysmal attacks, both histamine and phentolamine (regitine) may be used. When the patient has sustained hypertension, regitine alone is used, because it decreases blood pressure by blocking the pressor effect of epinephrine and norepinephrine in the blood if a pheochromocytoma is present.

Technique.—The pharmacologic tests are simple, and a clinician may do them in his office. First, with the patient lying comfortably, the blood pressure is observed for half an hour to obtain the correct basal value. This is highly important in the interpretation of the results after use of histamine or regitine.

Histamine Test.—As a preliminary to the histamine test, a cold pressor test is carried out by immersing one of the patient's hands well above the wrist in a pail (8 inches in height) containing water at 4° C., keeping it immersed for one minute and measuring the blood pressure in the opposite arm at fifteen, thirty and sixty seconds while the hand is in the water. The highest reading during this stimulus represents the lability of the blood pressure. If a patient has a history of having high blood pressure, such as 230 mm. of mercury systolic and 160 mm. diastolic, at one time and at another time a low blood pressure of perhaps 130/90, the blood pressure under basal conditions may be 130/90 and then increase to 230/160 while the hand is immersed in the cold water. Such a patient has an extremely labile blood pressure and in most instances will not have a pheochromocytoma. However, if the increase of blood pressure during the cold pressor test is much less, pheochromocytoma may be suspected.

This cold pressor test is an integral part of the histamine test, because it should be used as the measuring stick for the response of the blood pressure two minutes after an intravenous injection of histamine. A cold pressor test is not done when the diastolic blood pressure is 150 mm. of mercury or more.

Histamine is given only when the basal blood pressure is less than 170/110. The histamine test as done at the Mayo Clinic is as follows: 0.05 mg. of histamine base in 0.5 ml. of isotonic solution of sodium chloride is injected intravenously. Determinations of the blood pressure are made every thirty seconds for the next two minutes. During this time, the blood pressure always decreases thirty seconds after the injection of histamine if the material has entered the vein. Immediately thereafter, the blood pressure increases rapidly and usually reaches the maximum in two minutes. As soon as the histamine is injected, the needle is left in the vein, the empty syringe is removed and a syringe containing regitine is attached. If a pheochromocytoma is present, the

From the Section of Physiology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

Presented at the Symposium on Peripheral Vascular Disease co-sponsored by the Minnesota Heart Association and the Mayo Foundation, Rochester, Minnesota, September 25, 1957.

characteristic clinical signs and symptoms of a severe episode appear concomitantly with the increase in blood pressure; the increase in systolic pressure may range from 30 to 104 mm. of mercury above basal pressure, and that in diastolic pressure may be from 25 to 56 mm. If the increase in blood pressure is caused by release of pressor amines, the regitine can be injected at any time when the blood pressure becomes alarmingly high; within one minute this drug produces complete cessation of the clinical signs and symptoms and a sudden rapid decrease in the blood pressure. Thus, histamine can be given safely and two positive reactions will be noted. If the patient has only mild essential hypertension, the blood pressure will not increase so much after the injection of histamine, and the headache will not disappear nor will the blood pressure decrease rapidly after the injection of regitine. If regitine is given alone to a patient with labile hypertension between paroxysms, the blood pressure may not change in the presence of a pheochromocytoma because pressor amines are absent in the blood between attacks. Therefore, falsely negative results will be obtained.

Regitine Test.—For the patient who has sustained hypertension (a basal blood pressure above 170/110), 5 mg. of regitine is administered intravenously; in the presence of pheochromocytoma, the blood pressure should decrease at least 35 mm. of mercury systolic and 25 mm. diastolic in 4 minutes and then increase to approximately the previous basal level in 10 to 15 minutes. Regitine has a tendency in some patients to produce some decrease in blood pressure during the first 1 or 2 minutes in the absence of a pheochromocytoma, but the blood pressure then returns to a level that is considered negative for such tumors.

Precautions.—The question often arises as to what precautions may be necessary to obtain correct results in these pharmacologic tests. One difficulty may be a difference in the blood pressure of the two arms, which may give falsely positive results with either histamine or regitine. If the blood pressure in both arms is measured simultaneously, a truly negative reaction to histamine and regitine then will become apparent. On the other hand, if a pheochromocytoma is present, the positive response will be evidenced in both arms. Therefore, the blood pressure is measured routinely in both arms of all patients; if any disparity occurs, the blood pressure then is determined simultaneously in both arms during pharmacologic tests.

A second precaution concerns previous medication. Before any of these tests, administration of any sedative or narcotic should be prohibited for at least forty-eight hours and possible self-medication should be checked or the pharmacologic tests may yield falsely positive results. In patients who have paroxysmal hypertension, sedatives inhibit the increase of blood pressure during the cold pressor test that is the measuring stick. As a result, the increase of blood pressure during the histamine test may be greater than that during the cold pressor test, thus indicating the presence of a tumor that does not exist. In patients who have sustained hypertension, the administration of potassium thiocyanate, barbiturates, meperidine (demerol), morphine, chloral hydrate and probably many other sedatives may cause a decrease in blood pressure typical of that produced in the presence of pheochromocytoma after the intravenous administration of regitine. On the other hand, various antihypertensive drugs may produce falsely negative results in the pharmacologic tests in patients with pheochromocytoma. Since most of these drugs act longer than do the sedatives, the difficulties are even greater. I have observed three patients who were receiving antihypertensive drugs in whom the results of the regitine test were initially negative but later reversed to positive after use of these drugs was discontinued and in whom tumors were subsequently found at operation. The ideal time to do these tests is before any drugs are given. If this is impossible, the administration of antihypertensive drugs should be discontinued for ten to twelve days. Thus, if previous medication has not been used or if use of the drugs has been stopped for an adequate period, the histamine test yields clear-cut positive or negative results for patients who have paroxysmal hypertension and the regitine test gives unequivocal results for patients who have sustained hypertension. Furthermore, these results may be obtained in an hour, and the tests may be carried out by the clinician. More than one test always should be done before an operation is performed.

Chemical Tests: Pressor Amines

The chemical tests for pheochromocytoma discussed by Dr. Manger present pitfalls, just as do the pharmacologic tests, because some pheochro-

mocytomas may not secrete continuously. This is true in patients with paroxysmal hypertension and probably in some patients with sustained hypertension who have pheochromocytoma. Blood or urine collected when the tumor is not secreting will contain small or normal amounts of epinephrine and norepinephrine, which indicates no tumor. However, if the blood is obtained before and at the maximal increase of blood pressure during a histamine test, the pressor amines in the blood will be greatly increased in a patient with pheochromocytoma and a correct diagnosis can be made, as positive results in three tests then will be available (two pharmacologic procedures and one chemical). On the other hand, no significant increase of epinephrine or norepinephrine in the blood is noted after the intravenous injection of histamine in patients without pheochromocytoma.

Negative results may be obtained with the chemical test for urinary pressor amines in the presence of pheochromocytoma. One patient had exhibited negative results in several tests for urinary catecholamines done elsewhere. A regitine test at the clinic gave positive results for pheochromocytoma, and a significant increase of pressor amines was noted in the blood. An 80-gm. pheochromocytoma was found at operation.

In contrast, in certain conditions such as azotemia, jaundice and lymphoblastoma, fluorescent substances other than pressor amines are present in the blood and appear as increased amounts of "pressor amines" in the chemical test. In one patient with lymphoblastoma, the pharmacologic tests for pheochromocytoma gave negative results but the clinical findings and an increase of "pressor amines" indicated tumor. The patient was explored and later died; pheochromocytoma was not found at necropsy.

Patients receiving chlorpromazine (thorazine) may have increased levels of fluorescent substances other than pressor amines; one such patient with a high level of substances presumed to be pressor amines died and an adrenal tumor was not found. Tetracycline (achromycin) apparently causes the appearance of fluorescent substances other than pressor amines; extremely high levels (7.4 to 40 micrograms) of "pressor amines" were found in four patients receiving this antibiotic. After use of the drug was stopped for four to six days, decreased levels of "pressor amines" were present. One of these patients was explored and adrenal tumors were not found. It was significant that the regitine test gave negative results in these patients. A normal volunteer (Dr. Forester) took three doses of 250 mg. each of achromycin orally six hours apart. After the third dose, the "pressor amines" had increased from 1.9 to 6.9 micrograms. Other drugs also may have such fluorescent properties.

Two further difficulties in the measurement of pressor amines have arisen with the use of antihypertensive drugs. First, while pressor amines may be increased in patients with pheochromocytoma who are receiving antihypertensive drugs, evidence exists that these agents may depress the amount of pressor amines during their initial administration. However, growth of the tumor is not inhibited and, as it grows, the increase in blood pressure may be re-established, as well as an increase in the amount of pressor amines. Secondly, an annoying side reaction after the use of antihypertensive drugs is nasal stuffiness. Many vasoconstrictor substances are used locally to alleviate this difficulty. These substances produce high levels of pressor amines in the blood and increased amounts of catecholamines in the urine; such increases have been interpreted as an indication of pheochromocytoma. These local vasoconstrictor drugs produce a profound decrease in blood pressure that may persist for as long as forty minutes after the intravenous injection of regitine. This is in contrast to the situation in a patient who has a pheochromocytoma; in this instance, the decrease in blood pressure may be as great but the pressure begins to increase in four to five minutes and often approximates the basal level within ten minutes. The prolonged lowering of blood pressure after injection of regitine alerts the physician to the possibility that something other than a pheochromocytoma is producing the response.

Comment

It is apparent that no single test is adequate in testing for pheochromocytoma. The sedatives produce falsely positive results with histamine and regitine, whereas antihypertensive drugs produce falsely negative results. However, by discontinuing use of sedatives for forty-eight hours and of antihypertensive drugs for a week or more, reliable results with regard to pheochromocytoma can be obtained.

Under these conditions, a correct diagnosis can be made by pharmacologic tests. A total of 11,706

pharmacologic tests have been carried out on 10,623 patients at the clinic with no untoward effects. Pheochromocytomas have been correctly diagnosed and found at operation in fifty-seven patients.

Use of only the chemical test for pressor amines may be unreliable in the diagnosis of pheochromocytoma after administration of chlorpromazine, achromycin and perhaps other drugs unknown as yet, in patients with azotemia or jaundice, and in certain diseases such as lymphoblastoma. The same holds true in patients receiving vasoconstrictor drugs, such as patients with asthma or vasomotor rhinitis, or patients having the afore-mentioned side reactions from antihypertensive drugs. For the most part, use of drugs that influence the pressor amines must be discontinued for at least six days to obtain reliable results.

Summary

Correct results in pharmacologic and chemical tests for pheochromocytoma may be obtained if certain precautions are observed. Accurate determination of the basal blood pressure before the tests is necessary, as is discontinuance of previous medication, such as use of sedatives, narcotics and various antihypertensive drugs.

A cold pressor test is an integral part of the histamine test for pheochromocytoma. Simultaneous determination of blood pressure in both arms during either a histamine or a phentolamine (regitine) test will produce accurate results if blood pressure differs in the two arms.

Blood and urine collected for the chemical measurement of pressor amines shortly after a spontaneous attack or after induction of an attack by histamine contain increased amounts of pressor amines, which indicates the presence of pheochromocytoma. However, chemical tests alone are unreliable after the administration of chlorpromazine and tetracycline (achromycin) in patients with azotemia, jaundice or lymphoblastoma, and in patients receiving vasoconstrictor drugs, such as those with asthma or vasomotor rhinitis or those having side reactions from antihypertensive drugs.

When measures are taken to eliminate the situations that interfere with correct results and when full consideration is taken of the inherent potential shortcomings in the procedures, the use of both pharmacologic and chemical tests is of great value in the diagnosis of pheochromocytoma.

METHOD FOR DETECTING HEART LEAKS

A method for detecting hidden leaks in the valve between the left chambers of the heart has been developed by scientists at the National Heart Institute in Bethesda, Maryland.*

The new method has been described in technical detail in *The Journal of Clinical Investigation* (January, 1958) by cardiologists Eugene Braunwald and George H. Welch of the Institute's Laboratory of Cardiovascular Physiology, and surgeon Andrew G. Morrow of its Clinic of Surgery.

To reveal the leak, these investigators raise the arterial blood pressure by injecting the artery-constricting hormone, norepinephrine, into the patient's blood stream at a carefully measured rate. Meanwhile, they observe and record the effects of this increase in blood pressure on the pressure inside the left atrium.

A leaking valve is revealed if the pressure rises grossly in this chamber in response to the rise produced in the arterial blood pressure. In a normal heart, the pressure rise in this chamber is slight because such gross changes in arterial blood pressure are largely excluded from the atrium by a tightly closing mitral valve.

A combined condition of "stenosis" and "insufficiency" commonly affects the same mitral valve. The new diagnostic method is expected to be most useful against the combined condition, where the murmurs and blood pressure abnormalities of insufficiency are often masked by those of stenosis.

Detecting hidden mitral insufficiency before operating for stenosis may be of vital importance, because the valve-splitting operation usually performed for stenosis may actually worsen the heart trouble if the valve also tends to leak.

Following successful tests in dogs, the method was tried in twenty patients in the Heart Institute Clinic of Surgery. Seven of these had pure mitral insufficiency, seven had pure stenosis, and the other six had the mixed condition.

In the thirteen patients with insufficiency, norepinephrine caused the pressure in the atrium to rise momentarily to an average of 47.8 per cent of the rise in the arterial blood pressure—in some patients it went as high as 125 per cent. In the patients with pure stenosis, the increase in atrial pressure averaged only 8.5 per cent of the arterial pressure increase. This difference was great enough to form the basis for a method for detecting mitral insufficiency in difficult cases.

To record blood pressures in the left atrium, a slender filament of plastic catheter tubing was placed in the heart via the mouth, throat and windpipe—a catheterization technique called the "transbronchial puncture," introduced into the U. S. by Dr. Morrow. Dr. Morrow sprays the back of the patient's throat with novocain and then makes a puncture with a hypodermic needle at the point where the windpipe forks. He then threads the catheter through the bore of the needle into the atrium, which lies just below the fork. The needle is then withdrawn, allowing the patient to relax in comparative comfort, with one end of the flexible hollow thread of catheter in his heart and the other end emerging from his mouth to be attached to recording and sampling devices.

*The National Heart Institute is one of the seven National Institutes of Health that comprise the research arm of the U. S. Public Health Service.

The Treatment of Hypertensive Emergencies

JOHN H. MOYER, M.D.
Philadelphia, Pennsylvania

MARKED AND SUDDEN elevation in blood pressure, regardless of cause, may become a direct threat to the patient's life even though that elevation may be only a part of the clinical syndrome. Under these circumstances, reduction of the blood pressure may be the primary therapeutic objective.

Hypertensive emergencies require therapeutic agents that will reduce the blood pressure rapidly. The agents available for this purpose vary considerably in effectiveness, depending upon the etiology of the blood pressure elevation. For example, hydralazine is very dependable in the therapy of toxemia of pregnancy and acute glomerulonephritis. However, it is of little value in the treatment of so-called "malignant essential hypertension." Ganglionic blocking agents are useful for the treatment of an ambulatory patient with essential hypertension, but because they are primarily effective in the standing position, they are much less valuable for the therapy of the bedfast patient with a severe hypertensive crisis. Veratrum extracts, when administered parenterally, are effective in all types of hypertension (except pheochromocytoma), but due to the severity of the side effects, these compounds should be used only after the less potent agents have been tried. Thus, if these drugs are to be used to best advantage in the treatment of hypertensive emergencies of various etiologies, the therapist must be acquainted with the clinical pharmacology of the different agents. It is the purpose of this report to present a general approach to the treatment of hypertensive emergencies and to discuss some pertinent clinical pharmacodynamic problems.

Although the exact physiology underlying the majority of cases of hypertensive emergencies associated with essential hypertensive vascular disease is not known, the importance of the autonomic nervous system in its maintenance seems well-founded. It has been established that drugs that produce partial blockade at various points along the sympathetic pathways from the higher centers to the neuroeffector site will reduce the arterial blood pressure in these instances (Fig. 1), regardless of the degree of its elevation and without regard to the underlying cause of the hypertension.

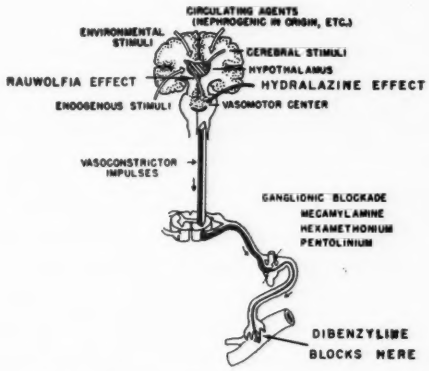


Fig. 1. Pharmacology of hypertension and antihypertensive agents used in the treatment of hypertensive emergencies. Rauwolfia and Hydralazine act centrally to depress vasoconstrictor impulses traveling from the brain to the blood vessels. Veratrum acts centrally as well as reflexively by stimulating afferent impulses in the heart and great vessels which are transmitted to the brain as vasodepressor reflexes. Following administration of the peripherally acting drugs, sympathetic impulses are blocked and the reduction in blood pressure is primarily in the orthostatic position.

The drugs used for the treatment of hypertensive emergencies may be classified on the basis of three sites of action within the sympathetic nervous system i.e., central, ganglionic, and adrenergic blocking agents:

(1) The most effective centrally-acting agents are extracts of Rauwolfia serpentina (reserpine rescinnamine and deserpidine), Veratrum preparations (cryptenamine, protoveratrine, alkavervir) and hydralazine (Apresoline) which suppress vaso-

Dr. Moyer is Professor of Internal Medicine, Hahnemann Medical College, Philadelphia, Pennsylvania.

Presented at the Symposium on Peripheral Vascular Disease co-sponsored by the Minnesota Heart Association and the Mayo Foundation, Rochester, Minnesota, September 25, 1957.

TABLE I. BLOOD PRESSURE AND SYMPTOMATIC RESPONSE

Continuous Infusions of Intravenous Veriloid for the Treatment of Severe Encephalopathy

Patient	Age	Known Duration (yr.)	Diagnosis	Pulse Rate		Blood Pressure			Side Reactions	Infusion Period (hr.)	Symptomatic Improvement (Encephalopathy)
				Control	During Infusion of Veriloid	Control Mean	During Veriloid Infusion				
							Mean	Range			
1	42	10	CN*	77	50	210/140	156/104	180/120-130/ 80	None	72	++
2	24	8	HCVD†	66	44	260/150	155/ 90	170/100-130/ 72	None	48	++
3	36	7	HCVD	82	80	300/210	180/125	200/140-150/110	Weakness	96	+++
4	51	2	HCVD	100	60	290/160	140/120	160/130-130/108	Hiccough, vomiting	24	+
5	28	13	CN	107	108	224/162	160/110	196/140-110/ 80	Restless	48	+++
6	48	1	HCVD	120	100	230/164	150/ 90	160/108-138/ 80	Dizzy, weak, nausea	48	+++
7	52	10	HCVD	80	64	248/130	162/ 90	180/104-148/ 82	Dizzy	48	+++
8	33	6	CN	90	70	190/120	110/ 66	130/100- 90/ 58	Vomiting	24	++
9	29	6	CN	80	64	220/160	130/ 95	150/108-110/ 90	None	18	Pt. died
10	27	4	HCVD	104	70	265/170	155/105	170/115-130/100	Vomiting	72	+++
11	60	7	HCVD	84	70	235/150	170/110	190/120-135/ 90	Nausea	72	+++
12	55	0.5	CN	100	50	225/145	180/130	200/140-170/120	None	96	+
13	48	0.3	HCVD	72	58	310/220	240/160	260/180-200/130	Weakness, hiccough	48	0
14	49	1	HCVD	84	76	200/140	130/100	158/115-120/ 80	Vomiting	24	0
15	53	2	HCVD	80	86	190/125	130/110	170/120-110/ 98	Hiccough, nausea	72	++
16	56	1	HCVD	76	72	240/162	150/100	170/110-140/ 96	None	96	0
17	54	1	HCVD	90	56	300/210	158/110	200/130-110/ 90	Hiccough, weakness	24	+++
Mean	44	4.7		88	69‡	243/159	156‡/107‡			55	

*CN—Chronic nephritis.
†HCVD—Hypertensive cardiovascular disease.
‡Statistically significant change from control values ($p<0.01$).
Courtesy, Moyer, et al: The American Journal of Medicine, 14:175, 1953.

TABLE II. COMPARISON OF CEREBRAL HEMODYNAMIC RESPONSE TO ACUTE BLOOD PRESSURE REDUCTION

With Various Agents in Hypertensive and Normotensive Subjects: Mean Values

Type of Patient	Drug Administered	Mean Blood Pressure mm. Hg.		Cerebral Blood Flow cc/min.		Cerebral Oxygen Consumption cc/min.		Cerebro-vascular Resistance		Arterial P CO_2		Number Patients Studied
		C	D	C	D	C	D	C	D	C	D	
Severe hypertensives	Phenoxybenzamine (dibenzyline)	149	82	48	42	3.6	3.1	3.2	2.2	40	40	7
Severe hypertensives	Alkavervir (veriloid)	173	108	57	50	2.9	3.4	3.2	2.3	39	37	10
Severe hypertensives	Dihydroergocornine	160	122	58	58	3.5	3.6	2.9	2.0	38	39	12
Normotensives	Hexamethonium	99	62	57	42	3.2	2.9	1.8	1.5	41	40	8
Normotensives	Dihydroergocornine	94	78	60	55	3.8	3.5	1.7	1.5	40	40	5

C=Control.
D=After drug.
Courtesy Moyer et al: American Journal of Medical Sciences, 228:563, 1954.

constrictor impulses at their sites of origin at or above the vasoregulatory centers.

(2) Ganglionic blocking agents, that is, hexamethonium (Methium), pentolinium (Ansolysen) chlorisondamine (Ecolid), mecamylamine (Inversine) and trimethaphan camphorsulfonate (Arfonad), act not only at sympathetic ganglia to block vasoconstrictor impulses but also at the parasympathetic ganglia to produce a variety of undesirable effects.

(3) The third major group of autonomic blocking agents are those that produce adrenergic blockade, such as phenoxybenzamine (Dibenzyline), at the neuroeffector site.

Pharmacodynamics

Cerebral function is improved by lowering the blood pressure in hypertensive patients, particularly if hypertensive encephalopathy exists (Table I). When the blood pressure is reduced, the cerebral vessels dilate, and cerebral blood flow and metabolism are maintained (Table II). When the blood pressure is reduced excessively, however, cerebral blood flow may decrease sharply. This is more frequently observed in the upright position when agents that block impulses at or beyond the ganglia are used, since reflexes responsible for adjusting peripheral vascular resistance to compensate for position change may be inhibited, with resultant excessive hypotension in the upright position. When this occurs, dizziness may be prominent. When, by excessive dosage, the supine blood pressure has been reduced to absolute normotensive levels with peripherally-acting agents, the patient should usually remain in bed; otherwise syncope may result when the patient stands up.

Generally, cardiac failure is improved following reduction of blood pressure. The initial response

after administration of the ganglionic blocking agents, if heart failure is not present, is an acute reduction in blood pressure (Fig. 2) with a reduction in cardiac work load and little effect on cardiac output. However, due to release of venous tone, venous pressure also decreases, followed by a reduction in venous return and subsequently in cardiac output (Fig. 2).

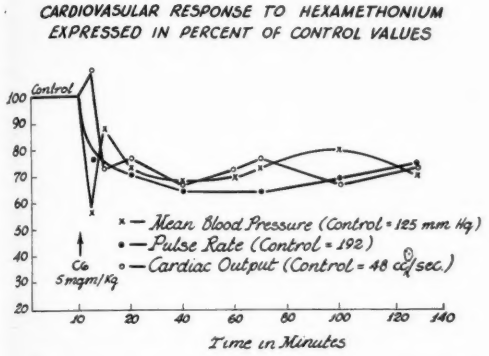


Fig. 2. Cardiovascular response to acute reduction in blood pressure with a ganglionic blocking agent, hexamethonium. There is at first a sharp decrease in arterial peripheral resistance. This is followed by venous dilatation, decreased venous return, and subsequently a reduction in cardiac output. (Courtesy: *Journal of Pharmacology and Experimental Therapeutics,* 106:157, 1952).

As a generalization, glomerular filtration rate and renal blood flow are depressed when the blood pressure is reduced acutely. One exception to this rule is hydralazine (Apresoline) which temporarily increases renal blood flow but does not alter or may reduce glomerular filtration rate (Fig. 3). Renal function is depressed (Fig. 4) more after the administration of the ganglionic blocking agents than it is following administration of the centrally-acting agents. When intravenous infusions of ganglionic blocking agents are continued, glomerular filtration rate and renal blood flow remain depressed throughout the period of infusion when the blood pressure is reduced to low normotensive levels. However, after intermittent parenteral administration (either intravenously or intramuscularly) there is a similar initial depression in renal function following which renal blood flow tends to return to control levels despite a persistent depression of glomerular filtration rate. After prolonged blood pressure regulation renal hemodynamic readjustment usually occurs following which renal function is no longer depressed (Fig. 4).

In patients with severe hypertension and associated renal disease, the reduction of the blood pressure must be approached cautiously. Patients with renal damage respond to blood pressure reduction in a way qualitatively similar to patients with normal kidneys, but the readjustment is

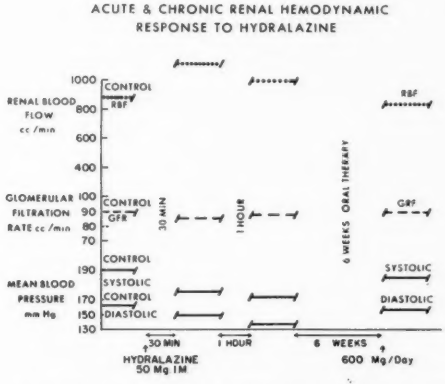


Fig. 3. Hydralazine administration increased renal blood flow at least temporarily. However, there was not a concomittant increase in glomerular filtration rate. Therefore, any beneficial effect on excretory function due to the Hydralazine on the kidney *per se* is not forthcoming.

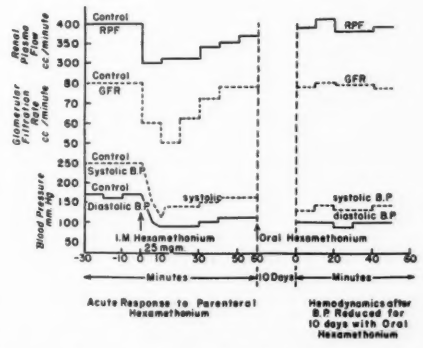


Fig. 4. The acute and chronic renal hemodynamic response to ganglionic blockade. There was a sharp reduction in glomerular filtration rate and renal blood flow. However, when the patient was later switched to oral administration and the drug was given over a long period of time, renal hemodynamic adjustment followed and despite the fact that blood pressure remained at normotensive levels, glomerular filtration rate and renal blood flow returned to the control levels. (Courtesy *American Journal of the Medical Sciences,* 225:379, 1953).

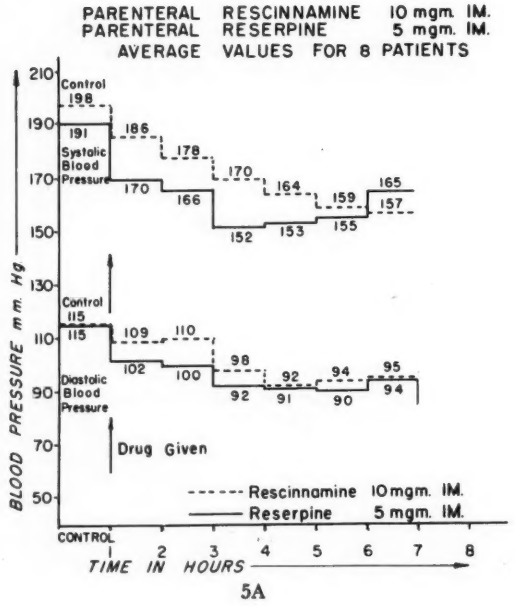
slower and incomplete. If readjustment is incomplete and if renal function is markedly impaired to begin with, even small reductions in glomerular filtration may be serious enough to produce renal decompensation. Incomplete renal hemodynamic readjustment is more likely to occur if blood pressure is suddenly reduced to absolute normotensive or hypotensive levels. This means that in patients with severe renal disease, extreme care must be taken in reducing the blood pressure. When the blood urea nitrogen (BUN) is 35 to 50 mg. prior to therapy, it is usually safe to acutely reduce the systolic pressure (to 160 to 180 mm. Hg.). If it is 50 to 80 mg. it is better not to reduce the systolic pressure much below 190 to 200 mm. Hg. When the BUN is above 80 to 100 mg. Hg., blood pres-

TABLE III. COMPARISON OF THE RENAL HEMODYNAMIC RESPONSE TO MECAMYLAMINE HEXAMETHONIUM AND PENTOLINIUM

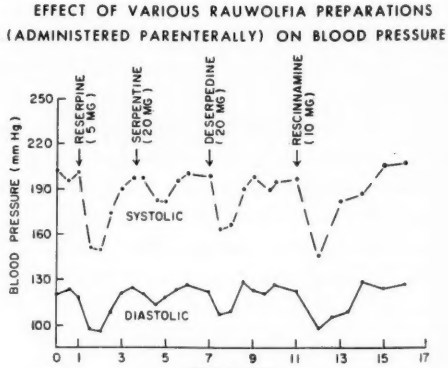
In Patients Receiving the Drugs for Prolonged Periods of Time

Drug	Number of Patients	Control	Drug	Per Cent of Control	P* Value	Tilt	Per Cent Drug Supine	P' Value
Mean Blood Pressure* (mm.Hg.)								
Mecamylamine	8	154	135	88	.001	109	81	.001
Hexamethonium	7	159	134	84	.001	104	78	.001
Pentolinium	11	146	118	81	.001	—	—	—
Glomerular Filtration Rate (ml./min.)								
Mecamylamine	8	80	68	85	.2	50	74	.01
Hexamethonium	7	73	71	97	.1	56	79	.02
Pentolinium	11	83	80	96	.1	—	—	—
Renal Blood Flow (ml/min.)								
Mecamylamine	8	809	704	87	.3	508	72	.01
Hexamethonium	7	801	815	102	.1	501	61	.01
Pentolinium	11	866	963	111	.1	—	—	—

*Mean Blood Pressure=Diastolic pressure plus one-third of pulse pressure.
Control=Control recumbent.
Drug=Drug recumbent.
Per Cent Control=Drug/Control x 100.
Per Cent=Tilt/Drug x 100.
P* Value=Comparison of Control with Drug; A P Value of less than .05 is significant.
Tilt=Tilted head-up position for mecamylamine and ambulatory state for hexamethonium.
P' Value=Comparison of Drug with Tilt.



5A



5B

Fig. 5A. A comparison of blood pressure response to Rescinnamine as compared to Reserpine. Although the dose requirement of Rescinnamine is one and one-half to two times that of Reserpine and the onset of action of Reserpine is less rapid, the degree of blood pressure reduction is equivalent. (Courtesy *American Journal of the Medical Sciences*, 231:542, 1956). B. Comparison of blood pressure response to four different alkaloid extracts of Rauwolfia given parenterally.

sure reduction can be rarely maintained without aggravating the renal failure. When encephalopathy is severe in these patients and if temporary reduction in blood pressure is mandatory, it is possible to lower the blood pressure intermittently but it is necessary to allow it to increase at regular intervals for the kidneys to function.

Clinical Use of Antihypertensive Drugs In Hypertensive Emergencies

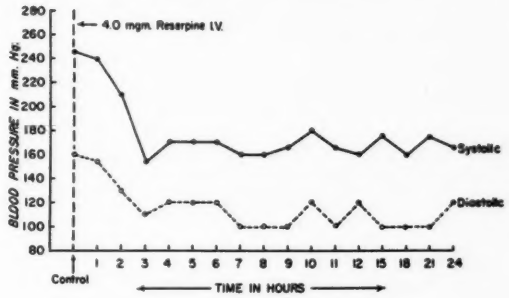
Central Agents

Rauwolfia Alkaloids.—Reserpine (Sandril, Serpasil, Serpiloid), and rescinnamine (Rescamine)—single alkaloids from Rauwolfia—when given in adequate doses parenterally, are probably the most useful antihypertensive agents available for the general treatment of hypertensive emergencies exclusive of the hypertension associated with pheochromocytoma. When given by the parenteral route, both agents are quite potent, in contrast to the response to the same drugs after oral administration (Figs. 5A and B). However, there is a latent period of one to two hours before the blood pressure decreases, following either intravenous or intramuscular administration.

Therefore, if immediate reduction in blood pressure is required, a more rapidly acting drug is indicated. Under these circumstances, in patients with a hypertensive emergency associated with essential hypertension, a ganglionic blocking agent or a Veratrum extract should be used initially and the reserpine or rescinnamine administered at the same time for maintaining the reduction in blood pressure. Following the initial reduction in blood pressure, these patients can usually be carried along with reserpine or rescinnamine, alone. Ganglionic blocking agents or Veratrum extracts are also indicated in patients who do not obtain an adequate reduction in blood pressure with parenteral reserpine.

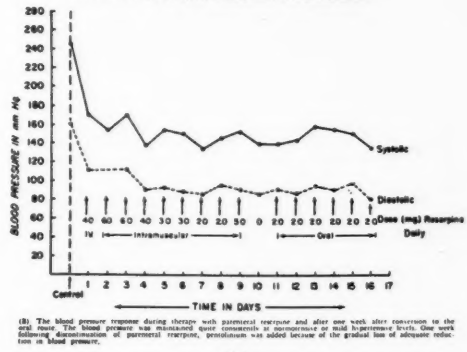
In patients with hypertension association with acute glomerulonephritis and toxemia of pregnancy, reserpine in combination with hydralazine or Veratrum is the therapy of choice. We have studied reserpine administered parenterally to patients with hypertensive emergencies associated with severe essential hypertension, as well as in patients with severe hypertension of renal origin due to renal artery occlusion, cystic disease of the kidney, and chronic pyelonephritis. The results achieved indicate that reserpine, when administered parenterally, is a relatively potent antihypertensive agent and there are few hypertensive patients who do not obtain a significant reduction in blood pressure. The antihypertensive effect is manifested in the recumbent position as well as in the upright position, an attribute of considerable importance in the acutely ill and bedfast patient. The slow decrease in blood pressure which occurs and the relative rarity of excessive reduction allows effective and safe therapy without particularly close supervision by medical and nursing personnel.

BLOOD PRESSURE RESPONSE TO 4.0 MGM. OF RESERPINE ADMINISTERED INTRAVENOUSLY TO A PATIENT (W.W.) WITH MALIGNANT HYPERTENSION



6A

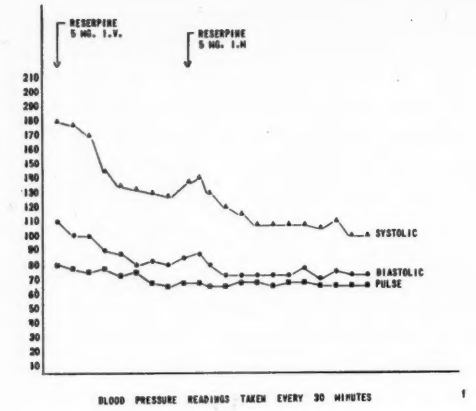
BLOOD PRESSURE RESPONSE TO PARENTERAL RESERPINE IN A PATIENT (W.W.) WITH MALIGNANT HYPERTENSION



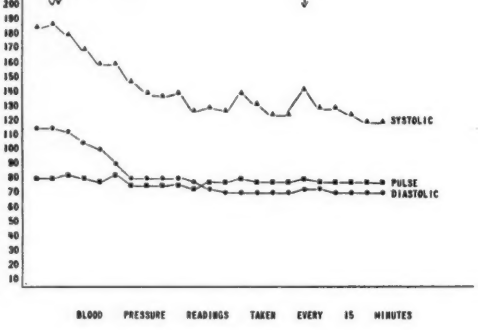
(B) The blood pressure response during therapy with parenteral reserpine and after one week after conversion to the oral route. The blood pressure was maintained quite consistently at normotensive or mild hypertensive levels. One week following discontinuation of parenteral reserpine, pentolinium was added because of the gradual loss of adequate reduction in blood pressure.

6B

Fig. 6A. A patient with malignant hypertension. The blood pressure response to 4 mg. of Reserpine administered intravenously. The onset of significant blood pressure reduction occurred two hours after the injection, and maximum reduction occurred at three hours. Significant blood pressure effect was still present after twenty-four hours. B. The blood pressure response during therapy with parenteral Reserpine and for one week after conversion to the oral route. The blood pressure was maintained quite consistently at normotensive or mildly hypertensive levels. One week following discontinuation of parenteral Reserpine, Pentolinium was added because of a gradual loss of adequate reduction in blood pressure. (Courtesy *A.M.A. Archives of Internal Medicine*, 95:7, 1955).



7A



7B

Fig. 7A. Blood pressure response to Reserpine in a patient with toxemia. B. Response in a patient with more severe hypertension in whom immediate blood pressure reduction was indicated.

The proper dose of reserpine given parenterally for the treatment of hypertensive emergencies is best determined on the basis of the blood pressure response to increasing doses starting with 2.5 mg. and increasing the dose in 2.5 mg. increments until an adequate reduction in blood pressure is obtained (Fig. 6A). At least two hours must be allowed between doses in order to observe the maximum response to any single dose. The drug may be administered intramuscularly or it may be given intravenously in 100 cc. of 5 per cent glucose given over a fifteen to thirty-minute period. The response varies in degree and duration in different patients, but there is very little difference between the intravenous and the intramuscular route in the same patient.

After the proper dose has been established, the patients are then placed on a regular schedule which usually consists of 5 to 10 mg. of reserpine given every six to twelve hours (Fig. 6B). The maintenance dose and the interval between doses depends entirely on the blood pressure response and is adjusted so as to maintain the desired blood pressure level. When excessive reduction in blood pressure occurs, a vasopressor agent is an effective antidote. Blood pressure, pulse rate and respiration should be recorded every thirty minutes following the initial doses, and as necessary following subsequent doses.

The side effects tend to become more prominent as either the dose of reserpine or the frequency of administration is increased. Muscle tremors and other manifestations suggesting a Parkinson's syndrome may appear if doses of 5 to 10 mg. are given as frequently as every six hours for an extended period of time, but these disappear slowly after a reduction in the dose or frequency of administration, or after discontinuation of therapy. Doses in excess of 40 mg. a day should not be employed.

Rescinnamine is a pure alkaloid obtained from Rauwolfia serpentina, and is similar to reserpine. When given intramuscularly, rescinnamine is equally as effective as reserpine (Figs. 5A and B), but the dose required is one and one-half to two times as great. There is essentially no difference in the incidence and severity of side effects of reserpine as compared to rescinnamine except somnolence is less marked with the latter. The manner of administration is the same for both agents except that we employ an initial dose of rescinnamine of 5 mg. given intramuscularly. If this is inadequate, the dose is increased to a maximum of 15 mg. given no more frequently than every six hours. Doses in excess of 60 mg. a day should not be used.

Hydralazine (Apresoline).—In the treatment of hypertensive emergencies, this drug is limited primarily to use in acute glomerulonephritis and toxemias of pregnancy. Best results are obtained when it is used in conjunction with reserpine. The onset of reduction in blood pressure (fifteen to twenty minutes) is more rapid after hydralazine than after the administration of reserpine. Therefore, it is given in cases with acute nephritis and toxemia of pregnancy where rapid onset of action is necessary, or in patients who do not respond adequately to reserpine alone.

TABLE IV. GENERAL OUTLINE OF ANTIHYPERTENSIVE THERAPY FOR THE TOXEMIA PATIENT CONFINED TO THE HOSPITAL

Severity of Disease	Hypotensive Drug Therapy	
	Reserpine	Hydralazine
Mild pre-eclampsia (blood pressure 140/90 to 160/100)	5 mg. I.M. or I.V.—may be repeated in 1-2 hours if still hypertensive. Thereafter, for maintenance, 5 mg. every 4-6 hours as needed for blood pressure of 140/90 or above.	Given only when normotensive response not obtained with reserpine alone—may give 5-10 mg. I.V. as single injection or slow I.V. infusion with 25 mg. placed in one liter of 10% dextrose in water.
Severe pre-eclampsia (blood pressure above 160/100)	10 mg. I.M. or I.V.—may be repeated in 1-2 hours if still hypertensive. Thereafter, for maintenance 5 mg. every 4-6 hours as needed for blood pressure of 140/90 or above.	10 to 20 mg. I.V. as single injection for rapid initial blood pressure fall if desired response not obtained from reserpine—then repeat only when unable to maintain normotensive on reserpine alone. May be given by continuous I.V. infusion, 50 mg. placed in one liter of 10% dextrose in water, when blood pressure labile or is difficult to get desired response as in labor.
Severe pre-eclampsia and primary hypertensive disease (blood pressure 160/100)	Same as for severe pre-eclampsia.	Same as for severe pre-eclampsia.
Eclampsia	10 mg. I.V. and repeat in 1-2 hours if still hypertensive; then give maintenance dose of 5-10 mg. every 4-6 hours to ensure sedation and a normotensive state.	If BP 170/100 or above, give 20 mg. single I.V. injection. If BP between 150/90 and 170/100, give 10 mg. single I.V. injection. If BP between 130/80 and 150/90, use continuous I.V. infusion of 25 mg. in one liter of 10% dextrose in water slowly, so that it may be discontinued quickly should the BP fall too low. If after the initial injections, the hypertension is very labile or difficult to control the continuous I.V. infusion of 50 mg. in one liter of 10% dextrose in water should be used.

TABLE V. RESPONSE OBTAINED WITH RESERPINE ALONE AND IN COMBINATION WITH HYDRALAZINE
303 Patients with Toxemia of Pregnancy

Diagnosis	Total Number Patients	Good		Fair		Poor	
		Number	Per Cent	Number	Per Cent	Number	Per Cent
Severe pre-eclampsia	95	85	89	10	11	00	0
Primary hypertensive disease with severe pre-eclampsia	25	23	92	2	8	0	0
Mild pre-eclampsia	169	153	91	16	9	0	0
Eclampsia	14	14	100	0	0	0	0
Total	303	275	91	28	9	0	0

When hydralazine is administered in patients with hypertension due to toxemia of pregnancy, an initial dose of 5 to 20 mg. should be given intravenously as a single injection over a five-minute period or intramuscularly in a dose of 10 to 25 mg. Then 25 to 50 mg. (depending on severity) should be placed in 1000 cc. of 10 per cent glucose in water and be given by continuous intravenous infusion (Table IV). The rate of infusion should be adjusted depending on the blood pressure response. When given parenterally, there is usually a pronounced fall in bood pressure within twenty minutes, the reduction being most marked in the diastolic pressure. The effect may last up to twelve hours. The general approach to antihypertensive therapy in toxemia of pregnancy is outlined in Table IV.

Of 303 patients with toxemia of pregnancy treated by the author and his colleagues, 211 responded adequately to parenteral reserpine, alone (Table V). Eighty-nine patients received a combination of reserpine and hydralazine. With this approach, blood pressure has been well controlled in over 90 per cent of patients (Table V).

TABLE VI. PARENTERAL RESERPINE
Approximate Individual Dose

Average Age Years	Weight		Dose—Mg.	
	Pounds	Kilograms	Average	Maximum*
1	22	10	1.0	1.5
3	34	15	1.5	2.0
5	44	20	2.0	3.0
9	66	30	3.0	4.5
12	88	40	4.0	6.0
14	110	50	5.0	7.5
Adult	150	70	7.0	10.0

*This is the maximum effective dose.

In patients with acute nephritis, the blood pressure may be elevated initially or it may not appear until the third or fourth day of the disease. In our experience, the ideal drug for reducing the blood pressure in patients with acute nephritis is parenteral reserpine used alone or in combination with hydralazine. The reserpine is given intramuscularly as described previously. In children the dose is usually regulated according to the weight of the child (Table VI). The blood pressure is usually reduced to a safe range, but rarely does it become entirely normal. When adequate antihypertensive effect is not obtained with reser-

pine alone, then a supplement of hydralazine should be added, but the reserpine continued as the basic agent.

In certain patients parenteral reserpine either fails to give ideal antihypertensive effect (Fig. 8)

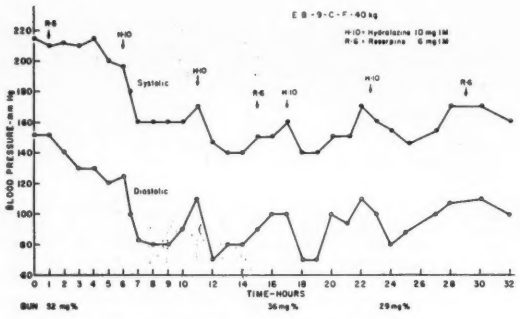


Fig. 8. Patient with acute nephritis. The response to Reserpine (R-6) was not adequate and it became necessary to administer Hydralazine (H-10).

or else the critical state of the patient's cardiovascular reserve demands a more rapid reduction of blood pressure. The addition of single doses of hydralazine is usually effective. This combined approach permits the use of smaller, and therefore safer, doses of hydralazine.

In the patients who have already received reserpine, and who show inadequate antihypertensive effect, it is our custom to begin by administering a 5 mg. dose of hydralazine (intravenously or intramuscularly). Then the blood pressure is measured every fifteen minutes. If less than the desired fall in bood pressure occurs within forty-five minutes, the supplemental dose of hydralazine is increased by 5 mg. increments until blood pressure control is achieved (Fig. 9). The dose thus established is used thereafter as often as necessary, as a supplementary drug to control blood pressure. In this way, a titration of the effective dose is carried out *in vivo*. We have preferred the intramusclular administration of hydralazine. In the patient who is admitted with convulsions, or other evidence of hypertensive encephalopathy, the simultaneous administration of intravenous reserpine and hydralazine may be necessary.

Veratrum Drugs.—When a ganglionic blocking agent (when used in combination with parenteral reserpine) is also ineffective in hypertensive emergencies one can then use a continuous intravenous infusion of alkavervir (veriloid) or protoveratrine (veralba). Such Veratrum extracts are the most potent antihypertensive agents available today, and it is rare that a patient will not respond to these drugs. However, because they usually pro-

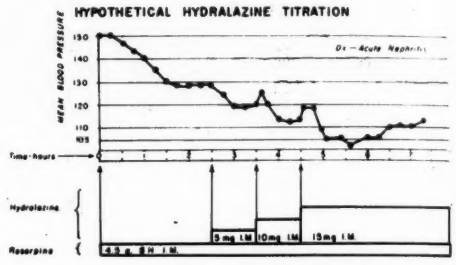


Fig. 9. Dose titration of Hydralazine in children with acute nephritis.

duce nausea and vomiting and because of their potency and the difficulty of regulating the blood pressure when these agents are used, they should be employed only as a last resort and only in those patients who do not respond to more simple methods of treatment. These drugs are as effective in the supine as in the upright position, a virtue of note.

Parenteral alkavervir (veriloid) is one of the most dependable centrally-acting veratrum extracts which can be given either intramuscularly or by continuous intravenous infusion. The onset of action is rapid, that is, within several minutes. When using this drug, great caution must be exercised because the blood pressure can easily be lowered excessively. It also produces a rather marked reduction in pulse rate by vagal stimulation (Fig. 10). It may produce nausea and vomiting in many cases in which an effective reduction of blood pressure has been obtained. The incidence of side effects is high when adequate amounts of this agent are used to reduce the blood pressure to normotensive levels (Table I). For example, in one study conducted by the author, nausea or vomiting was observed in seven out of seventeen patients. Despite the high incidence of side reactions, some improvement in the encephalopathic manifestations exhibited by these patients was observed in all but four patients and in seven of the seventeen cases, all manifestations of encephalopathy cleared following an effective and maintained reduction in blood pressure (Table I).

When used intravenously, an initial priming dose of alkavervir is given which consists of 0.5 microgram per kilogram body weight per minute over a twenty-minute period (Fig. 10). The blood pressure should be checked every minute during

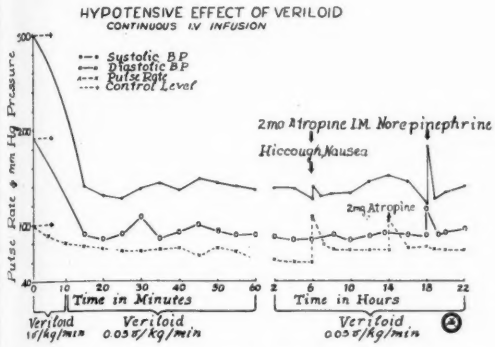


Fig. 10. Blood pressure response to alkavervir (Veriloid) administered intravenously in a patient with malignant hypertension.

this time and until an adequate reduction in blood pressure is obtained. A change is then made to the sustaining infusion (Fig. 11). The priming dose is prepared by diluting 10 micrograms per kilogram body weight of intravenous solution of alkavervir in 20 cc. of 5 per cent glucose in distilled water. If the desired hypotensive effect has not been achieved with the initial priming dose, it may be repeated at least in part. The sustaining solution consists of 4 mg. of alkavervir added to a liter of 5 per cent glucose in distilled water. This is given at a rate that is regulated depending on the amount necessary to maintain the desired blood pressure level. As a precaution, a similar infusion containing 4 mg. of norepinephrine per liter of 5 per cent glucose in distilled water should be prepared beforehand and connected through a Y-Tube (Fig. 11) for immediate infusion should the blood pressure decrease excessively at any time. Norepinephrine is a very effective antidote.

During the initial period of adjusting the rate for a sustained infusion of alkavervir or protoveratrine, the blood pressure and pulse rate should be checked every two or three minutes for the first thirty minutes and then every five minutes until the blood pressure is completely stabilized. The blood pressure should be checked every fifteen to twenty minutes throughout the entire period of intravenous infusion. This requires the full-time attendance of a nurse or someone well trained in the use of these drugs who is capable of taking blood pressures properly. As soon as feasible, oral or intramuscular hypotensive therapy should replace the intravenous infusion (Figs. 12A and B).

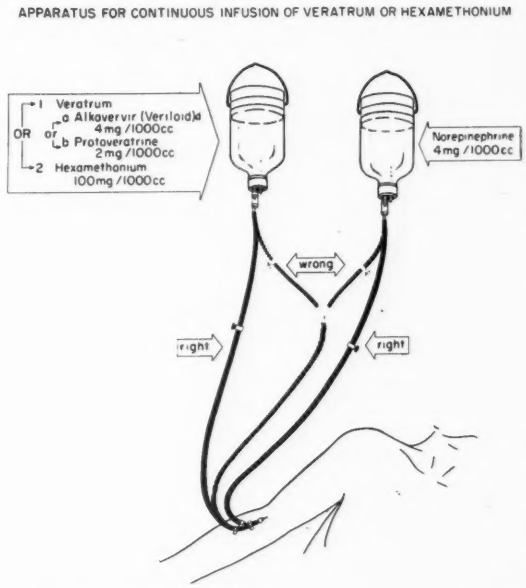
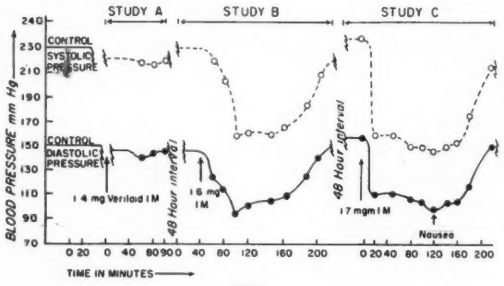


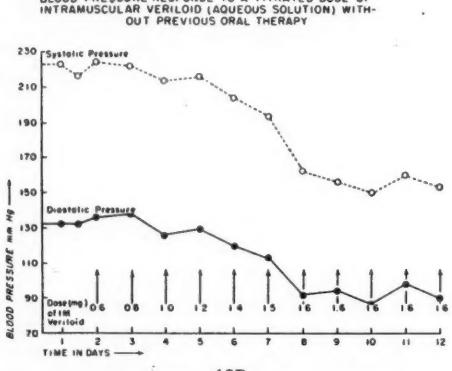
Fig. 11. Method of setting up a continuous infusion for the administration of Veratrum or ganglionic blocking agents. When using either alkavervir or protoveratrine, it is necessary to have a vasopressor agent available for immediate administration should excessive reduction in blood pressure occur.

When the route of administration of alkavervir is changed from the intravenous to the intramuscular one, the first intramuscular dose should be 0.6 mg. given every four to six hours (Figs. 12A and B). The dose should then be increased in 0.2 mg. increments until significant reduction in blood pressure occurs (Figs. 12A and B) after which the dose should be increased more gradually (usually in about 0.1 mg. increments) until the blood pressure is reduced to the desired level. Then the frequency of administration is adjusted depending upon the length of action of the drug as reflected in the length of time the pressure remains reduced. The blood pressure should be recorded at least every fifteen minutes until the dose is well adjusted following intramuscular administration of the drug. Norepinephrine or a similar vasopressor agent should be available at

the bedside at all times in the event that excessive hypotension occurs. Atropine, in a dose of 1 mg. is very effective in combatting excessive bradycardia. There is no effective antidote for the



12A



12B

Fig. 12A. When the blood pressure is brought under control with an intravenous infusion of Veratrum, then the drug can be administered by the intermittent intramuscular route. When this is done the dosage must be titrated until an effective reduction in blood pressure has occurred. B. Demonstration of dosage titration of Veriloid in overall blood pressure response of a patient with malignant hypertension. (Courtesy *American Journal of the Medical Sciences,* 226:477, 1953).

nausea and vomiting that may be associated with veratrum administration.

Intravenous protoveratrine (veralba 0.2 mg./cc.) is probably as effective as alkavervir. The priming solution is made up by diluting 0.5 cc. (0.1 mg.) of protoveratrine in 10 cc. of 5 per cent glucose. This diluted solution is then injected at a rate of 0.5 cc./minute. If there is no fall in blood pressure after five minutes, the procedure is repeated. When the desired decrease in blood pressure has been obtained, a continuous intravenous infusion of 2 mg. of protoveratrine (one ampule) in 500 cc. of glucose (5 per cent) solution is then administered. The infusion rate is adjusted as necessary in order to achieve the desired blood pressure level without vomiting—usually 40 to 80 drops per ten minutes. The blood pressure should be checked at least every fifteen minutes after the blood pressure has become stabilized.

After the immediate emergency is over, the intramuscular route of administration may be employed. For this purpose, give 0.6 cc. (0.12 mg.) intramuscularly and check the blood pressure every fifteen minutes. The maximum effect occurs in one to two hours. Repeat with increments of 0.2 cc., added or reduced, every four to six hours depending on the patient's response. Atropine is effective for the bradycardia but not for nausea or vomiting. If excessive reduction in blood pressure occurs, a vasopressor drug is effective.

Ganglionic Blocking Agents

When reserpine (administered parenterally) is ineffective in patients with other than acute nephritis and toxemia of pregnancy, then a ganglionic blocking agent such as hexamethonium, pentolinium (Ansolysen), trimethaphan camphorsulfonate (Arfonad) or mecamylamine (Inversine) should be tried either alone or in combination with reserpine. When given intramuscularly, they are safe and usually effective therapeutic agents, and the danger of excessive reduction in blood pressure is not as great as with Veratrum administered parenterally. The frequency of administering intramuscular ganglionic blocking agents will depend on the length of time that the blood pressure remains reduced following each dose. As soon as the hypertensive emergency is under control, the patient should be started on oral therapy.

As in ambulatory patients, care must be exercised in reducing the blood pressure in patients with renal failure lest the renal function be further impaired. The best estimate of adequate renal functional capacity is gained by repeated determinations of the blood urea nitrogen. If the blood pressure is reduced excessively, it can be corrected by the administration of a vasopressor agent such as norepinephrine (Fig. 13) or any other readily available vasopressor agent that can be given intravenously or intramuscularly.

The blood pressure response to ganglionic blocking drugs is most marked in the standing position, which is one of their greatest shortcomings.

Thus, these agents are of limited value in the bedfast patient who is supine. In patients with severe disease, an adequate reduction in blood pressure is sometimes impossible, necessitating the use of Veratrum extracts. It is not good to give excessive doses of ganglionic blocking agents with the idea of "forcing the blood pressure down" since frequently the result will be a severe ileus due to blockade of the parasympathetic ganglia without obtaining the desired reduction in blood pressure.

Assistance in blood pressure reduction can be obtained if the head end of the bed is raised on blocks. Usually 10 to 12 inch blocks are effective, but the farther the head end of the bed is raised, the better. If large doses of the drug have been given and a marked orthostatic effect obtained, careful attention must be given to the degree of blood pressure reduction obtained when the patient is tilted. Otherwise, excessive hypotension can occur, resulting in cerebral ischemia and cerebral anoxia.

When constipation becomes a problem, cathartics and cholinergic agents should be used freely. Cascara sagrada in a dose of 15 cc. to 30 cc. or milk of magnesia in doses of 30 to 60 cc. is usually adequate. Cholinergic agents are sometimes more effective than cathartics. For this purpose, 15 to 45 mg. of prostigmine or 5 to 10 mg. of pilocarpine given orally three or four times a day is usually adequate. If the patient is comatose, 1 mg. of prostigmine is used subcutaneously; when ileus is present, 1 mg. should be given every hour until peristalis returns. When treating hypertensive emergencies, mecamylamine is of limited value for bedfast patients because of the persistence of the blockade and resultant constant and frequently severe constipation. When this drug is used, particular attention must be given to the bowels, and cathartics or cholinergic agents must be used freely.

When giving hexamethonium by continuous intravenous infusion for hypertensive emergencies 100 to 150 mg. are placed in 1000 cc. of 5 per cent glucose in distilled water. The drug is infused at a moderate rate until the blood pressure begins to fall, then the rate of infusion is adjusted so as to maintain an adequate reduction in blood pressure. As a safety precaution the infusion apparatus should be connected to a Y-tube such as in Fig. 11. Norepinephrine is an effective antidote for hexamethonium, as well as all other ganglionic blocking agents, should excessive reduction in blood pressure occur. The blood pressure and pulse rate should be checked at least every five minutes during the initial period of adjustment. After the blood pressure has been stabilized it should be checked every fifteen to twenty minutes.

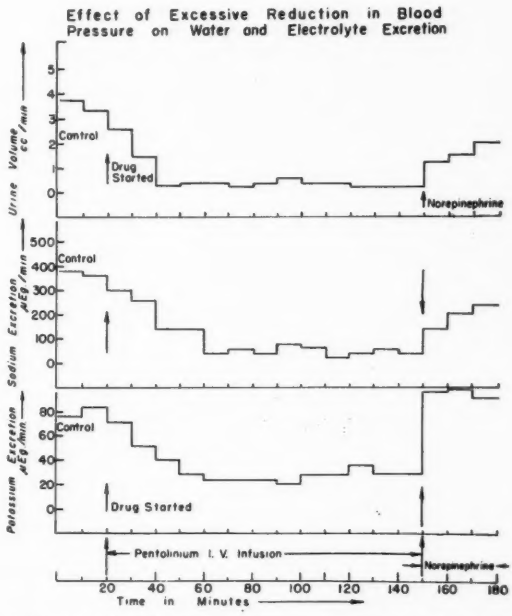


Fig. 13. A patient in whom an excessive reduction in blood pressure was observed with Pentolinium (Ansolysen). The patient became anuric due to a marked decrease in glomerular filtration rate. However, as the blood pressure was elevated with a vasopressor agent, glomerular filtration rate returned toward control levels and urine output also returned to previous values.

When administering hexamethonium intramuscularly, the initial dose is 15 milligrams. After waiting one hour to determine the effect of the initial dose, another dose is given, and subsequent doses are given in increasing amounts until an adequate effect is obtained. Usually, the drug can be repeated every one to two hours until effective reduction in blood pressure occurs. Doses in excess of 100 mg. are no more effective than this amount. The frequency of administering intramuscular hexamethonium will depend on the length of time that the blood pressure remains reduced after each injection. Usually, it is only necessary to give the drug every four to six hours. As soon as the hypertensive emergency is under control, the patient should be started on oral therapy. Care must be exercised in reducing

the blood pressure for patients with renal failure lest the renal function be impaired further. A systolic blood pressure of 170 to 180 mm. Hg. is usually a safe level unless the BUN is markedly elevated prior to therapy.

TABLE VII. GANGLIONIC BLOCKING AGENTS

Summary of Results in Patients Treated for Fulminating Heart Failure Associated with Severe Hypertension

	Hexamethonium	Mecamylamine (Inversine)	Arfonad
Number patients treated	16	8	11
Significant reduction in blood pressure	12	6	10
Normotensive	4	2	9
Improvement in pulmonary edema	13	7	10
Recovery	12	6	10

Pentolinium is used in essentially the same manner as hexamethonium. When making up the intravenous infusion, 50 to 75 mg. per 1000 cc. of 5 per cent glucose is adequate. The rate of infusion is adjusted according to the blood pressure response. When giving the drug intramuscularly, an initial dose of 5 mg. is used. After one to two hours, the second dose is given, and so on until an adequate reduction in blood pressure is obtained. Usually, the second dose is 10 mg. and the subsequent doses are progressively increased until the blood pressure has been adequately controlled or a maximum of 50 mg. per dose is given. If the blood pressure is not reduced adequately with 50 mg. per dose or less, given intramuscularly, it is rarely possible to obtain an increased response with doses in excess of this amount. The same problems exist with this drug as have been noted in the use of hexamethonium.

Mecamylamine is completely absorbed from the gastrointestinal tract and consequently is as effective when given orally as when given parenterally. Therefore, when the patient is capable of taking medication orally, he can be given the same dose by this route as was found to be effective previously when given by the parenteral route. Complete absorption also allows reproducible blood pressure responses to equal doses of drug with minimum day-to-day variation, the lack of which is a serious drawback to the use of ganglionic blocking agents of the quaternary ammonium variety, such as hexamethonium and pentolinium.

The initial dose of mecamylamine is 3 mg. given intramuscularly or subcutaneously. This can be repeated every two hours and increased in 3 to 5 mg. increments until an adequate reduction in blood pressure is obtained. Doses in excess of 50 mg. produce no additional effect and should not be given. As with the other blocking agents, tilting the bed in the head-up position assists in reducing the blood pressure. The frequency of administration will depend on the length of time the drug remains effective, frequently twelve to eighteen hours. As with pentolinium and hexamethonium, if the blood pressure is reduced excessively, the glomerular filtration rate may become markedly depressed. Therefore, when this occurs, it is necessary to administer a vasopressor agent.

Ganglionic blocking agents are particularly useful in patients with severe and acute heart failure associated with sudden elevation in blood pressure (Table VII). As therapeutic blockade is established, there is a reduction in venous tone, resulting in a decrease in venous pressure and venous return, followed by an increase in cardiac output. The relief of pulmonary edema is often dramatic.

In hypertensive patients without heart failure, cardiac output decreases, apparently due also to a decrease in venous tone and subsequent reduction in venous return. The significance of the reduction in cardiac output and untoward effects resulting therefrom in the patient without heart failure are not known to me. Certainly there is no harm done since I am not aware of aggravation or precipitation of heart failure from the judicious use of ganglionic blocking agents.

When used in patients with hypertension and fulminating heart failure, hexamethonium or pentolinium can be given intravenously in a concentrated solution in order to avoid extra fluid administration (Figs. 14A and B). An initial dose of 25 mg. of hexamethonium or 10 mg. of pentolinium in 1 to 10 cc. of fluid is usually preferable. This dose can be increased and repeated after thirty minutes or as frequently as necessary to reduce the blood pressure. After an effective blood pressure reduction has been obtained, hexamethonium must usually be given every two to four hours, pentolinium every six to eight hours, and mecamylamine (5 to 10 mg.) every eight to ten hours. For maintenance therapy, the drugs are usually given intramuscularly.

Arfonad (trimethaphan camphorsulfonate) is useful in patients with fulminating pulmonary edema because it is more effective in reducing the

arterial blood pressure than the other ganglionic blocking agents (Table VII). An additional attribute is that it is effective for only short periods of time so that the degree of blockade and blood pressure reduction can be regulated from minute to minute. However, it must be given as a continuous intravenous infusion.

Peripherally Acting Agents

Phenoxybenzamine is an effective adrenergic blocking agent which can be given intravenously (but not intramuscularly). However, because of the complete blockade (both humoral and at the end organ) produced by this drug, rendering vasopressor agents ineffective, it is generally thought inadvisable to administer this blocking agent by the parenteral route. Should excessive reduction in blood pressure occur with the use of this agent, no effective antidote is available. When its use becomes mandatory, 30 mg. is placed in 500 cc. of 5 per cent glucose in distilled water. Should excessive hypotension occur, the patient should be tilted in a 20 to 25 degree head-down position and the drug should be discontinued. *Do not infuse norepinephrine since this drug will only potentiate the hypotension.*

When taken by mouth, phenoxybenzamine is absorbed rapidly, and the effect lasts twelve to eighteen hours. It is useful in a few cases of severe hypertension and in the temporary management of patients who are not yet ready for surgery but who suffer from severe hypertension due to pheochromocytoma.

Phentolamine (Regitine) is useful for the treatment of patients with severe hypertension due to the liberation of norepinephrine by a pheochromocytoma. When used for this purpose, it is administered as a temporary measure for controlling the blood pressure prior to and during surgical removal of the tumor. A dose of 5 mg. of phentolamine is given intravenously or intramuscularly and is repeated as frequently as necessary in order to control the blood pressure.

If for any reason the patient must be treated for prolonged periods, the blood pressure can usually be better controlled with phenoxybenzamine given by the oral route. The dose of phenoxybenzamine by this route is 10 mg. every six hours. The dose is then subsequently increased in 10 mg. increments until effective reduction of the blood pressure is obtained. This method of therapy should be considered a temporary expedient only, since this is a curable disease, and the tumor should be surgically removed as soon as possible.

Ganglionic blocking and centrally-acting antihypertensive agents are not only ineffective in treating pheochromocytoma, but may actually precipitate an acute rise in blood pressure since these agents do not block the ability of norepinephrine to constrict the arterioles.

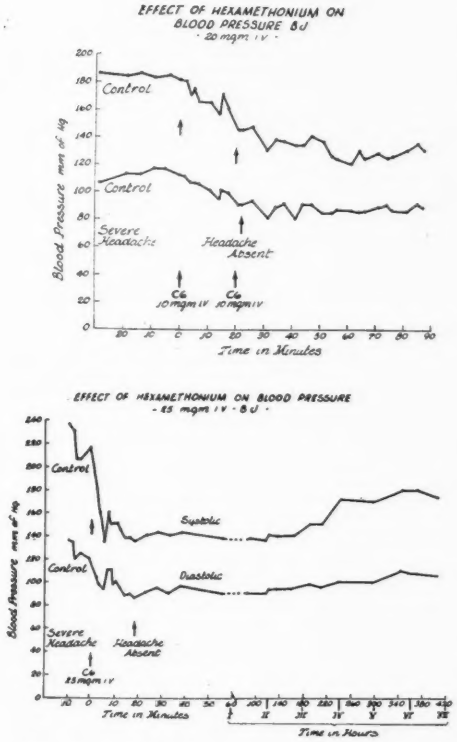


Fig. 14A. Blood pressure response to hexamethonium in a patient with mild hypertension. B. Blood pressure response to hexamethonium in a patient with severe hypertension.

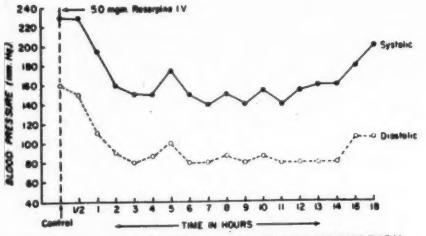
Special Considerations

Primary Renal Disease (Excluding Nephritis).—As indicated previously, even the patient with primary renal disease may benefit from blood pressure control if severe hypertension becomes an important component of his disease. A case example is summarized in Figure 15. This was a patient who developed marked atherosclerosis of the aorta which also involved the right renal artery resulting

in acute occlusion of the artery due to thrombus formation. The left renal artery was not involved.

At the time of admission to the hospital, the patient had marked encephalopathy, retinal hem-

BLOOD PRESSURE RESPONSE TO 5 MGM OF RESERPINE ADMINISTERED INTRAVENOUSLY TO A PATIENT (G.L.M.) WITH MALIGNANT HYPERTENSION ASSOCIATED WITH OCCLUSION OF THE ABDOMINAL AORTA AND LEFT RENAL ARTERY



RENAL FUNCTION RESPONSE FOLLOWING HOMOGRAPH IN PATIENT WITH GOLDBLATT KIDNEY

	Glomerular Filtration Rate ml/min. Right (occluded)	Left	Renal Blood Flow ml/min. Right (occluded)	Left
Control	0	25	0	130
Blood Pressure Rx.	0	35	0	200
Homograph				
1 month	0	45	0	425
8 month	0	60	0	725

Fig. 15. Blood pressure response in a patient who had a sudden onset of malignant hypertension due to occlusion of one renal artery. This patient responded to Reserpine in the same way that a patient with essential hypertension does. As the blood pressure remained reduced, glomerular filtration rate in the unoccluded kidney increased and after six months of therapy the glomerular filtration rate and renal blood flow had returned to normal for one kidney. The blood urea nitrogen over this period of time decreased from a level of 70 mg. per cent to 30 mg. per cent. (Courtesy *A.M.A. Archives of Internal Medicine,* 98:427, 1956).

orrhages, papilledema, and he was convulsing as a result of malignant hypertension, probably secondary to the ischemic kidney ("Goldblatt Kidney"). He was placed on parenteral reserpine given every six hours. This effectively reduced the blood pressure, and most of the cerebral manifestations subsided. He was gradually switched to a combination of oral Rauwolfia and a ganglionic blocking agent, mecamylamine. The aorta was replaced by a homograft but the kidney was not removed due to the poor condition of the patient. The postoperative course was uneventful and the blood pressure has since been well regulated for a period of three years and the patient is now in full-time employment.

This patient had no return of renal function in the occluded kidney (right). However, in the opposite kidney (left), glomerular filtration rate and renal blood flow, which were depressed to less than 50 per cent of normal for one kidney prior to therapy, gradually increased so that now they are approximately normal. His blood urea nitrogen has decreased from 70 to 30 milligrams per 100 cc. of blood.

Undoubtedly the depression in function in the unoccluded left kidney was due to severe vasoconstriction, intrarenal hemorrhages, and acute vascular damage, rather than chronic deterioration. Since the process was relatively acute, it was partially reversible. Had the hypertension and increased sympathetic vasoconstrictor response been allowed to continue, progressive renal failure would have developed had the patient not died first of cerebral manifestations.

Therefore, even in the patient with primary renal disease and hypertension secondary thereto, benefit can be derived from effective antihypertensive therapy. These patients should be treated in the same way as patients with hypertension associated with so-called essential hypertension are treated. If these patients are first seen in a state of crisis, they should receive parenteral reserpine. If more potent agents are necessary, one of the parenterally-administered Veratrum Compounds is used.

As soon as the emergency is brought under control, the diseased kidney should be removed if the problem is that of unilateral disease. If surgery is not feasible (as in the case of cystic disease of kidney or chronic pyelonephritis), the patient should be placed on a regimen of Rauwolfia given orally in combination with a ganglionic blocking agent and treated similarly to the patient with severe essential hypertension. Naturally, in the case of chronic pyelonephritis, it is mandatory that the etiologic organism be identified and treated with a specific antimicrobial agent.

Pheochromocytoma.—This has been described adequately elsewhere in this symposium.

Acute Steroid Hypertension.—The best treatment of acute hypertension associated with steroid administration is withdrawal of the steroid. However, in patients with severe and malignant disease such as lupus erythematous and leukemia, this is not possible. Therefore, it sometimes becomes necessary to continue the steroids and treat the

TABLE VIII. OUTLINE FOR ANTIHYPERTENSIVE TREATMENT OF HYPERTENSIVE EMERGENCIES

Emergency	Initial Therapy				Adjunctive Therapy When Initial Drug Inadequate	Maintenance Therapy After Emergency Over
	Drug	Dose	Route	Frequency		
Encephalopathy	Reserpine	2.5 to 10 mg.	I.M.	4-12 hours	Hexamethonium 10-100 mg. I.M. If inadequate then veriloid titration I.V. infusion	Rauwolfia+ganglionic blocking agent
	or Rescinnamine	5 to 15 mg.	I.M.	4-12 hours		
Fulminating heart failure	Hexamethonium	10 to 100 mg.	I.M.	30 min. to 4 hours	Reserpine I.M. or veriloid titration by I.V. infusion	Rauwolfia+ganglionic blocking agent
	or Arfonad	Titration	I.V.	Continuous infusion		
Intractable angina with severe hypertension	Hexamethonium		I.M.	1-4 hours	Reserpine 2.5 to 10 mg. given I.M.	Rauwolfia+ganglionic blocking agent
Hypertensive crisis	Reserpine	2.5 to 10 mg.	I.M.	4-12 hours	Hexamethonium 10-100 mg. I.M. If inadequate response then veriloid by I.V. infusion	Rauwolfia+ganglionic blocking agent
	or Rescinnamine	5 to 15 mg.	I.M.	4-12 hours		
Malignant hypertension of renal origin*	Reserpine	2.5 to 10 mg.	I.M.	4-12 hours	Hexamethonium 10-100 mg. I.M. If inadequate response then veriloid by I.V. infusion	Rauwolfia+ganglionic blocking agent
	or Rescinnamine	5 to 15 mg.	I.M.	4-12 hours		
Severe steroid hypertension	Reserpine	2.5 to 10 mg.	I.M.	4-12 hours	Veratrum, inversine, dibenzyline	Reserpine+veratrum+inversine and dibenzyline as required
Pheochromocytoma	Regitine	5 mg.	I.M.	p.r.n.	Dibenzyline 10-20 mg. orally	Surgery
Renal failure (uremia)	None				None	None

*Cystic disease, pyelonephritis, renal artery occlusions, etc.

hypertension as it develops. None of the current programs are very effective.

Reserpine should be given a trial. As in the treatment of hypertensive emergencies associated with essential hypertension, if this is not adequate, parenteral Veratrum should be used. Ganglionic blocking agents appear to be the least useful for this therapeutic problem.

As soon as the blood pressure is brought under control, oral therapy should be instituted. Alseroxylon (Rauwiloid) in combination with Veratrum or a ganglionic blocking agent is most useful. The Veratrum should first be given a trial, and the dose must be titrated. If nausea and vomiting ensue before the blood pressure effect is obtained, it is then necessary to use a ganglionic blocking agent. The dose is also established by titration. A combination of centrally-acting agents, with a ganglionic blocking agent, and an adrenergic blocking agent will sometimes be effective when the usual methods have failed. Each of the three agents is titrated up to tolerance or until the blood pressure is reduced adequately. Recently, we have observed that chlorothiazide (Diuril) given in a dose of 500 mg. every twelve hours will markedly increase the effectiveness of these agents.

Summary

In the approach to a patient with a hypertensive emergency associated with severe essential hypertension, it is necessary first to appraise the state of renal compensation, particularly if cerebration is abnormal. This can best be done with an estimate of the blood urea nitrogen (BUN). If the blood urea nitrogen is normal, renal failure is not likely to be responsible for any disturbances in the sensorium. Retinal examination is essential also. Retinal hemorrhages indicate the degree of general arteriolar damage. Papilledema suggests increased intracranial pressure and cerebral edema, which frequently accounts for derangement of cerebral function in patients who do not have associated renal failure.

After the state of renal function is known, therapy should be approached systemically (Table VIII). If immediate blood pressure reduction is not indicated and a delay of two to three hours is possible, parenteral reserpine or rescinnamine is the drug of choice. The initial dose is 2.5 mg., repeated in two hours if blood pressure reduction is not adequate. When the blood pressure is not reduced adequately at a maximum dose of 10 mg. of reserpine or 15 mg. of rescinnamine, given every six hours, a ganglionic blocking agent should be tried. There is very little difference in responsiveness among the different ganglionic blocking agents. I prefer hexamethonium for initial therapy because of its shorter duration of action and because it can be given intramuscularly. If the response does not appear beneficial, the drug can be discontinued with the loss of blockade in two to three hours.

In the case of fulminating heart failure a continuous infusion of Arfonad is probably the ther-

apy of choice if hexamenthonium is not adequate. Care must be taken so that excessive fluid is not administered. If ganglionic blockade appears to be adequate, one of the longer acting agents can be substituted for the hexamethonium after two or three days. This allows for less frequent administration. Mecamylamine is a particularly good substitute since, after dose adjustment, and when the patient's sensorium becomes clear, it is possible to switch to the oral route of administration employing the same dose of the drug as was effective by the parenteral route.

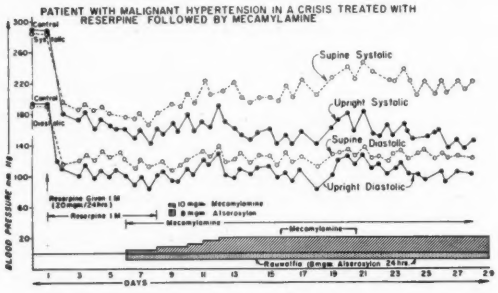


Fig. 16. Patient with malignant hypertensive encephalopathy who required parenteral Reserpine for initial reduction in blood pressure. After the blood pressure was regulated and the encephalopathic manifestations cleared, the patient was transferred slowly to a combination of Rauwolfia and a ganglionic blocking agent (Mecamylamine) administered orally. The blood pressure reduction was greatest in the standing position while receiving the latter agent. (Courtesy *A.M.A. Archives of Internal Medicine,* 98:427, 1956).

When ganglionic blocking agents given in combination with reserpine are not adequate, parenteral Veratrum should be given. Continuous intravenous infusion is the most potent and most effective approach, but the intramuscular route is preferred when full-time competent nurisng care is available, since excessive hypotensive episodes are less likely to occur following intramuscular administration.

After the hypertensive emergency is over and the blood pressure has been stabilized for three to seven days and the general status of the patient seems adequate, a permanent type program for blood pressure regulation should be substituted for the parenteral medication. A combination of Rauwolfia and a ganglionic blocking agent is usually the therapy of choice. Rauwolfia given by the oral route should be substituted for the parenteral reserpine. A dose of 1 mg. of reserpine, 250 mg. of the whole root or 4 mg. of alseroxylon, is usually given. After several months, this dose can be

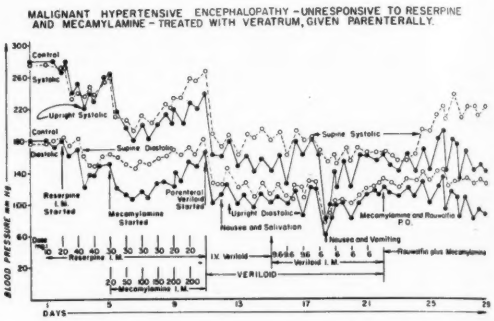


Fig. 17. Treatment of a hypertensive crisis in a patient who did not obtain an adequate response to Reserpine or to ganglionic blocking agents administered parenterally. A sharp and consistent reduction occurred when Veratrum was administered intravenously, but nausea was seen. The blood pressure was controlled with parenteral Veratrum; following this the cerebral manifestations cleared up. The patient was then transferred to a combination of Rauwolfia and Mecamylamine given orally. On this combination the blood pressure reduction was primarily in the orthostatic position, in contrast to the response when Reserpine was given, as well as when the alkavervir (Veriloid) was given by continuous infusion. (Courtesy *A.M.A. Archives of Internal Medicine,* 98:427, 1956).

decreased until the smallest effective dose is being employed.

As the effect of the parenteral reserpine is lost, one of the blocking agents is started and the dose gradually increased. The dose of the blocking agent must be adjusted according to the standing blood pressure (Fig. 16). It is preferable to have the patient completely ambulatory while adjusting the drugs administered orally.

When the BUN is elevated, this determination should be repeated every two or three days while the blood pressure is being regulated. When evidence of rising blood urea nitrogen is observed, the pressure should be allowed to increase slowly by decreasing the dose of the blocking agent until the blood urea nitrogen again decreases to pretreatment levels. As the blood pressure is controlled for prolonged periods, progressive vascular deterioration is usually arrested, and renal function will usually improve if it has not progressed beyond "the point of no return" prior to therapy.

Newer Concepts in the Treatment of Hypertension

RAY W. GIFFORD, JR., M.D.
Rochester, Minnesota

SINCE the advent of new and more effective hypotensive drugs, it is more than ever incumbent on the physician to determine which patients need treatment and to individualize the program of treatment so that the best results may be obtained with the least side effects. Moreover, access to effective palliative treatment does not excuse the physician from seeking potentially curable causes for hypertension, such as coarctation of the aorta, pheochromocytoma, primary aldosteronism, and unilateral renal disease.

Administration of potent hypotensive drugs should be preceded by adequate evaluation of the cardiovascular and renal systems, for such data have an important bearing not only on the choice of drugs but also on the prognosis. Numerous determinations of blood pressure should be made over an extended period, because insufficient pretreatment data on blood pressure are often responsible for unnecessary, misguided or erroneously evaluated treatment.

Choice of Patients for Treatment

No magic formula exits to guide the physician in choosing the patient who needs specific hypotensive treatment. Some physicians advocate treatment for all patients with hypertension, whereas others treat only those whose hypertension is complicated or symptomatic. The introduction of effective medical treatment for hypertension has been too recent to allow this dispute to be settled with finality, but rapidly accumulating experience indicates that the proper course lies closer to the former of these divergent opinions.

Hypertension may be uncomplicated or it may be complicated by the presence of hypertensive heart failure, coronary atherosclerosis with or without myocardial infarction, cerebral vascular insufficiency with or without cerebral infarction, cerebral hemorrhage and renal insufficiency. True hypertensive headache is considered to be a symptom and not a complication of hypertensive vascular disease for, unlike the others, it apparently has no bearing on prognosis.

Uncomplicated Hypertension.—When essential hypertension is uncomplicated, the best single criterion for determining the prognosis is the appearance of the optic fundi. The prognosis is so poor for patients who manifest the findings of Group 3 or Group 4 hypertensive retinopathy[1] that vigorous hypotensive therapy is urgently indicated even in the absence of complications or symptoms.

Patients with retinal findings of Group 1 or Group 2 hypertension, without cardiovascular or renal complications, have a relatively favorable prognosis. Therefore, some physicians prefer to observe these patients, employing such measures as mild sedation, adequate rest and reduction of weight, if indicated, and withholding specific hypotensive drugs. It is logical that patients in this group who have consistently high diastolic pressures are in more urgent need of treatment than are patients whose blood pressure is more labile.

The age and sex of the patient also must be taken into consideration in deciding which patients need treatment. By and large, women tolerate hypertension better than men do. It is a clinical impression that elderly patients, especially those who have high systolic and relatively normal or only slightly increased diastolic pressures, do not often get into trouble because of the hypertension. Treatment is usually advisable for patients whose family histories reveal that hypertension has frequently led to complications and untimely death among relatives.

In the final analysis, each physician must satisfy his own conscience in deciding to what extent the patient is to be inconvenienced by treatment for

From the Section of Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.
The Mayo Foundation is a part of the Graduate School of the University of Minnesota.
Presented at the Symposium on Peripheral Vascular Disease co-sponsored by the Minnesota Heart Association and the Mayo Foundation, Rochester, Minnesota, September 25, 1957.

TABLE I. PREPARATIONS OF RAUWOLFIA SERPENTINA AND THEIR DOSES

Preparation	Daily Dose (Single or Divided), mg.
Whole root (raudixin)	100-500
Alseroxylon fraction (rauwiloid, rautensin)	1.0-6.0
Reserpine (single alkaloid; preparations include serpasil, reserpoid, sandril, rau-sed, serpiloid)	0.1-1.0

a disease causing no symptoms. In arriving at this decision, the physician should ask himself two questions: (1) If he were the patient, would he want treatment? (2) Why do insurance companies "rate up" or refuse to insure hypertensive applicants, even though the hypertension is asymptomatic and uncomplicated? Furthermore, it behooves any physician who withholds hypotensive treatment from a patient to follow that patient closely, so that progression of the hypertensive vascular disease can be detected early, before it has led to irreversible complications.

Complicated Hypertension.—In the absence of overt evidence of coronary insufficiency, hypertensive heart disease manifested by significant cardiomegaly, with or without congestive heart failure, is an indication for prompt reduction in blood pressure.

It is surprising that patients whose hypertension is complicated by symptomatic coronary or cerebrovascular insufficiency usually tolerate gradual and cautious reduction of blood pressure without manifesting increased symptoms of myocardial or cerebral ischemia. Occasionally, it is advisable to start anticoagulant therapy for such patients before an attempt is made to reduce their blood pressure. Many hypertensive patients who have coronary insufficiency and angina pectoris derive considerable symptomatic improvement from treatment with hypotensive drugs. It is probably inadvisable to reduce the blood pressure of patients who have had cerebral or myocardial infarction within the previous six weeks, unless the blood pressure is extremely high and causing cardiac embarrassment. After the acute phase of the infarct has passed, hypotensive therapy is indicated.

Cerebral hemorrhage is an indication for prompt and drastic reduction of blood pressure, at times to hypotensive levels. Reduction of the blood pressure of patients whose hypertension is complicated by renal failure and azotemia often fails to improve the renal function; indeed, at times it appears to impair it further. However, the prognosis is so uniformly poor when azotemia supervenes that little is to be lost by a cautious trial of treatment.

Choice of Drugs

With the bewildering array of proprietary preparations, including confusing combinations of drugs in one tablet, now being marketed for the treatment of hypertension, it is well to remember that only four classes of drugs, exclusive of sedatives and tranquilizers, are of sufficient importance to warrant discussion. The specific hypotensive drugs to be discussed always should be administered in conjunction with, and not in lieu of, the less specific but time-honored and proved measures of reduction of weight, rest, relaxation, reassurance and sedation.

The choice of drugs and their doses must be individualized to meet the needs of each patient, for it is perilous to treat hypertension by stereotyped rules. For this reason, the use of tablets containing combinations of drugs is to be deprecated.

Rauwolfia.—An adequate trial of one of the derivatives of Rauwolfia serpentina is justified in most cases of hypertension when specific therapy is indicated. Since its hypotensive effect is neither drastic nor prompt, this agent should not be relied on as the sole hypotensive drug when prompt reduction in blood pressure is compulsory, unless it is given in relatively large parenteral doses (3 to 5 mg.). Doses of this size should not be administered for more than a few days. There is no evidence that any one preparation of Rauwolfia is superior to others (Table I). Side effects include nasal stuffiness, drowsiness, bradycardia, mild laxation, weird and bizarre dreams, Parkinsonian-like rigidity and mental depression. Only the last two effects are of such serious import as to compel prompt cessation of treatment. A previous history of mental depression or even a tendency toward mental depression constitutes a relative contraindication to the use of Rauwolfia, for major depression requiring electroshock therapy has been induced by these preparations. Rauwolfia should be administered cautiously, if at all, in the presence of an active peptic ulcer, since it increases gastric acidity.

Hydralazine (Apresoline) Hydrochloride.—Hydralazine hydrochloride produces a high incidence of unpleasant side reactions, including headache, nausea, vomiting, flushing, tachycardia, peripheral edema, fever and arthralgia. For this reason, it is seldom used alone, but it is excellent in combina-

TABLE II. PREPARATIONS OF VERATRUM AND RECOMMENDED DOSES

Preparation	Daily Total Dose (Usually Divided into Four Doses)
Whole powdered Veratrum viride (vertavis)	30-90 Craw units
Extract of ester alkaloids of Veratrum viride, such as alkavervir (veriloid) and cryptenamine tannate (unitensen)	8-24 mg.
Purified alkaloids of Veratrum alba, such as protoveratrines A and B (veralba) and protoveratrine A and B maleates (provell maleate)	0.8-3.0 mg.

TABLE III. GANGLION-BLOCKING AGENTS AND DOSES

Drug	Single Dose, mg.	Doses per 24 Hours
Hexamethonium chloride (methium, hexameton)	125-1,500	4 or more
Pentolinium tartrate (ansolysen)	20-500	3-4
Chlorisondamine chloride (ecolid)	12.5-200	2-3
Mecamylamine hydrochloride (inversine)	2.5-30	2-3

tion with Rauwolfia when hypertension cannot be adequately controlled with Rauwolfia alone. It also can be used advantageously in combination with a ganglion-blocking drug in the treatment of severe hypertension. Unfortunately, many physicians have been alarmed by reports of a collagen or "lupus" type of reaction resulting from prolonged administration of hydralazine in large doses. Clinically, this reaction resembles disseminated lupus erythematosus, and L.E. cells have been found in the blood of patients with this syndrome. The symptoms subside when the drug is withdrawn, and this reaction infrequently occurs when the daily dose of hydralazine does not exceed 200 mg. The usual single dose of hydralazine is 25 or 50 mg. given three or four times a day.

Veratrum (Table II).—All preparations of Veratrum now available share the glaring disadvantage of an extremely narrow margin between therapeutic and toxic doses. When Veratrum is used alone in the treatment of hypertension, toxic effects may appear before a therapeutically effective dose has been reached. The toxicity of Veratrum is unpleasant, although seldom dangerous. It consists of crises characterized by bradycardia, salivation, hiccup and heartburn, often followed by nausea and vomiting. Hypotension is an inconstant feature of a crisis induced by use of Veratrum. Consequently, it is advantageous to use Veratrum in combination with Rauwolfia or hydralazine or both, because it is often possible to obtain adequate reduction of the blood pressure with a minimum of side effects by using small doses of two or more drugs.

Ganglion-Blocking Drugs (Table III).—Unequivocally, the most potent hypotensive drugs available today belong to the group of ganglion-blocking agents. Because of their potency and side effects, administration of these drugs is not without danger and requires expert supervision by the physician, as well as the careful and often tedious cooperation of the patient. For these reasons, treatment with ganglion-blocking agents should be reserved for those patients in whom it is compulsory that hypertension be controlled promptly. These include patients with Group 3 or Group 4 hypertensive retinopathy and patients whose hypertensive vascular disease has progressed in spite of treatment with combinations of less potent drugs in adequate doses. Because of their specific action in reducing central venous pressure, the ganglion-blocking agents are especially helpful when hypertensive heart disease has led to congestive heart failure.

It is usually advisable that treatment be instituted and dosage adjusted while the patient is hospitalized. Treatment is started with the smaller doses shown in Table III, and each dose is changed by increments equal to the initial dose every second or third day until the blood pressure is satisfactorily controlled or until side effects preclude further increments. Certain patients may tolerate effective doses of one drug better than another, but this can be determined only by trial. It is preferable to give ganglion-blocking drugs at regular intervals, usually every six, eight or twelve hours, depending on the response of the blood pressure.

Experience has shown that treatment with ganglion-blocking agents is most effective when the patient or a member of his family or both have been instructed in the technique of measuring blood pressure, since in most cases the blood pressure must be used as a guide to make appropriate modifications in doses from day to day. For instance, patients are instructed to omit the ganglion-blocking agent whenever the systolic blood pressure is less than 120 mm. of mercury at the designated time for a dose. When the systolic blood pressure is between 120 and 140 mm. of mercury, only half the dose is taken. This is analogous to the situation in which a diabetic patient tests his urine for sugar as a guide

TABLE IV. PHARMACODYNAMICS OF GANGLION-BLOCKING AGENTS

Site of Block	Observed Effects	Antidote or Treatment
Sympathetic ganglia	Orthostatic hypotension	Reduce dosage; recumbent position
	Excessive hypotension	Elevate foot of bed; pressor drugs (neosynephrine, levarterenol)
Parasympathetic ganglia	Blurred vision	Pilocarpine eye drops; use of a positive lens
	Oral dryness	Pilocarpine nitrate (5 mg.) with each dose; chewing gum
	Constipation	Laxatives; prostigmin bromide (15 mg. sublingually or orally) as needed
	Paralytic ileus	Stop use of drug; prostigmin methylsulfate (1.0 mg. IM); intubation
	Urinary retention (older men)	Prostigmin bromide (15 mg. sublingually or orally); urecholine chloride (5 to 10 mg. orally); void before each dose; prostatic resection
	Impotence	Omit occasional dose

to dosage of insulin. To eliminate as many variables as possible, patients are instructed to take their blood pressures while sitting and to use the same arm each time.

Mecamylamine (inversine) hydrochloride is the only drug of this group that is absorbed completely from the gastrointestinal tract. This accounts for the rather small dose of this preparation compared to that of the others.

Drugs of this group reduce blood pressure by blockade of the autonomic ganglia of the sympathetic nervous system. Unfortunately, the blocking action of these drugs on the parasympathetic ganglia is also evident, and this gives rise to most of the undesirable and untoward side effects (Table IV). Patients can be reassured that many of these side effects diminish or disappear with prolonged use of the ganglion-blocking agent. Suggestions to alleviate some of these side effects are presented in Table IV. The number of patients who must abandon use of these drugs because of side effects bears an inverse relationship to the time which the understanding and sympathetic physician is willing to take to encourage his patients during the first few weeks of treatment. Special care must be taken to insure that patients who receive ganglion-blocking drugs have regular bowel movements, since paralytic ileus is a dangerous and occasionally fatal complication of treatment with these agents. Mecamylamine is the only one of this group of ganglion-blocking drugs that has been reported to produce a bizarre coarse tremor and psychosis. Hexamethonium is the only one of the group that has produced fatal interstitial pneumonitis. When these rare side effects occur, the patients so affected almost always are azotemic.

The concomitant use of Rauwolfia or apresoline or both with ganglion-blocking agents sometimes makes it possible to achieve smooth and effective reduction in blood pressure with smaller doses of the ganglion-blocking drug. This will eliminate or ameliorate some of the side effects.

Sympathectomy for Hypertension

Lumbodorsal sympathectomy usually is reserved for those patients whose blood pressure cannot be controlled by adequate doses of hypotensive drugs or whose temperament is such that they cannot tolerate or will not adhere to a strict medical regimen for the treatment of their hypertension.

Objectives of Treatment

The ultimate objective of the treatment of hypertension is to prevent or forestall the complications that cripple or kill. In the light of present knowledge, it appears that this can be accomplished best by reducing the blood pressure to normal or to as nearly normal a level as the patient can tolerate. The best immediate criterion, then, for the success or failure of treatment is the response of the blood pressure. Treatment should be pursued until the blood pressure is brought under satisfactory control or until side effects from the drugs preclude further increment in dosage. The limits of doses given in the tables are arbitrary and may be exceeded if necessary when the condition is resistant. If the blood pressure is not reduced, treatment is a failure and should be either abandoned or modified to produce the desired effect, for, so far as is now known, there is no virtue in administering ineffective doses of hypotensive drugs.

Results of Treatment

When the proper drugs or combinations of drugs are administered in adequate doses, blood pressure can be reduced significantly in most patients with hypertension. Reduction of blood pressure so achieved often produces astounding improvement in cardiac function and hypertensive retinopathy. Cardiac enlargement recedes, electrocardiographic evidence of left ventricular strain may disappear, signs and symptoms of congestive heart failure abate, and angina pectoris may improve remarkably. The retinopathy of malignant hypertension regresses with regularity. Hypertensive headache usually diminishes in severity or disappears entire-

ly. The lives of many patients with Group 3 or Group 4 hypertensive retinopathy undoubtedly have been prolonged by adequate medical treatment.

However, insufficient time has elapsed since the advent of effective hypotensive treatment to permit any conclusions with regard to the prolongation of life for patients with the retinal findings of Group 1 or Group 2 hypertension.

It is discouragingly clear that many patients whose hypertension is adequately controlled continue to suffer from, and all too frequently succumb to, those complications of hypertension that arise from coexisting atherosclerosis, namely cerebral and myocardial infarction. It is reasonable to assume, of course, that such complications result from extensive cerebral or coronary atherosclerosis that was present before blood pressure was controlled. More time must elapse and more patients must be treated during the early phase of their hypertension to determine whether adequate control of blood pressure will indeed retard atherogenesis.

Most disappointing is the failure of hypotensive therapy to influence beneficially the course of renal insufficiency, once this complication has occurred.

Disadvantages of Present Drug Therapy

Drug therapy of hypertension, although more effective now than ever before, is expensive, time-consuming for both patient and physician, and fraught with many unpleasant side effects, some of which are serious. Moreover, treatment is palliative and not curative, implying that it is a lifelong proposition. Physicians become dismayed when patients abandon an otherwise successful regimen because it is tedious and unpleasant. But discontent on the part of physicians is good, for it keeps them constantly searching for a more convenient, a more effective and a safer way to deal with the omnipresent problem of hypertension.

Reference

1. Keith, N. M.; Wagener, H. P.; and Barker, N. W.: Some different types of essential hypertension: Their course and prognosis. Am. J. M. Sc., 197: 332-343 (Mar.) 1939.

PRESSOR AMINES IN PHEOCHROMOCYTOMA

(Continued from Page 296)

was not found. After operation, the concentration of epinephrine-like substance was 2.6 and 1.9 micrograms per liter of plasma five and seven days, respectively, after the last use of nebulized epinephrine. At the time these blood samples were obtained after operation, results of the regitine tests were also normal. It was thought that absorption of epinephrine from the pulmonary parenchyma may have been sufficiently slow and the excretion impaired enough, as evidenced by a pre-operative blood urea of 70 mg. per 100 ml., to result in these increased concentrations of pressor amines.

A number of therapeutic agents undoubtedly may interfere with the chemical or biological assay of pressor amines, or with both techniques. Only with constant vigilance and by repeatedly investigating the effects of various therapeutic agents *in vitro* and *in vivo* on the fluorometric method of analysis and on the plasma concentrations of epinephrine and norepinephrine can one avoid drawing erroneous conclusions from the results of such fluorometric quantitation.

It was found essential in one of the patients with sustained hypertension and two of the patients with paroxysmal hypertension to obtain blood during or shortly after a paroxysm of hypertension, either naturally occurring or induced by anesthesia or a drug such as histamine, in order to increase the pressor amines to a concentration suggesting a diagnosis of pheochromocytoma. The percentage of norepinephrine in the plasma obtained pre-operatively was greater than that of epinephrine in all but three of the afore-mentioned twenty-three patients. This finding is consistent with the greater concentrations of norepinephrine than of epinephrine noted in the majority of tumor extracts. However, no close correlation was apparent between the percentage of pressor amines in the plasma and that in the tumors.

References

1. Weil-Malherbe, H. and Bone, A. D.: Chemical estimation of adrenaline-like substances in blood. Biochem. J., 51:311-318 (June) 1952.
2. Manger, W. M., Baldes. E. J., Flock, Eunice V., Bollman, J. L., Berkson, Joseph and Jacobs, Martin: A method for quantitative estimation of epinephrine and norepinephrine: Preliminary report. Proc. Staff Meet., Mayo Clin., 28:526-531 (Sept. 23) 1953.

Segmental Occlusion of the Femoral Artery and Femoral and Popliteal Aneurysms

Surgical Aspects

DAVITT A. FELDER, M.D.
THOMAS O. MURPHY, M.D.
Minneapolis, Minnesota

THE MAJORITY of patients presenting themselves with the complaint of intermittent claudication of the lower extremities could be afforded little, if any, relief until recently. While lumbar sympathectomy has given some relief of symptoms due to ischemia and has often prolonged the life of extremities, it has only infrequently provided relief from intermittent claudication.

The more recent direct surgical approaches (restoring direct continuity of blood flow or with by-pass technique) have resulted in restored muscle function to the point of relief from intermittent claudication. These newer methods have also resulted in healing of gangrenous areas in the more ischemic limbs or, in many instances, allowing for a lower level of amputation than might otherwise have been possible. In the case of occluding arterial lesions, the indications for surgery often are incapacitating claudication, if not other manifesations of ischemia. The possible loss of a limb seems to be a readily accepted risk in the patients with severe ischemia.

When an asymptomatic aneurysm of either the femoral or popliteal arterial vessels is found, the indications for surgery somehow seem to be less urgent, both to the patient and often to the physician, as well.

The report of Gifford, Hines, and Janes,[1] on the analysis and follow-up of 100 popliteal aneurysms, showed that twenty of these developed an acute thrombosis, sixteen ruptured, fourteen were responsible for distal emboli and twenty-four were the cause of a distal gangrene.

Even after thrombosis, repeated distal embolism, episodes of leakage and in spite of impaired function and of the obvious threat of recurrence with more serious consequences, the patient and often his physician, has hesitated to allow surgical treatment. The question heretofore has always been whether the surgical treatment might not make matters worse.

The aneurysmorrhaphy procedure of Matas,[2] which he performed in 154 instances, reduced the incidence of gangrene, in his series, from 10 per cent to 5.2 per cent. This report, however encouraging, did little to popularize surgical treatment of arterial aneurysms of the lower extremity.

In 1946, Lilly[3] proposed the procedure of lumbar sympathectomy followed by endaneurysmorrhapy. In three of his four cases he did a chemical sympathectomy using alcohol injections with good results. In the fourth patient he extirpated a ruptured aneurysm, after lumbar sympathectomy, also with a good result. It became apparent then, that one might perform a lumbar sympathectomy on patients with popliteal aneurysm and shortly therafter remove the aneurysm with relative impunity.

Stimulated by this, Linton[4] resected popliteal aneurysms in fourteen patients after preliminary sympathectomy without the loss of any limbs. This method, leaves the patient with a viable extremity, free from the threat of aneurymal rupture, embolism and thrombosis as brought out again in the detailed report of Gifford, Hines and Janes.[1] However safe, most of these limbs have impairment in function, in the form of intermittent claudication, as revealed by Julian and his associates.[5] This then, puts these limbs into the category with other arteriosclerotic lesions, in which restoration of adequate arterial blood flow is the ideal to be attained.

From the Vascular Surgical Services at the University of Minnesota Hospitals, Minneapolis General Hospital, Minneapolis, and Ancker Hospitals, St. Paul, Minnesota.

Dr. Felder is Clinical Associate Professor of Surgery, University of Minnesota. Dr. Murphy, formerly Instructor in Surgery, University of Minnesota, is now located in Tacoma, Washington.

Presented at the Symposium on Peripheral Vascular Disease co-sponsored by the Minnesota Heart Association and the Mayo Foundation, Rochester, Minnesota, September 25, 1957.

Failures and disappointments in this country, based on the experience of those who have attempted extensive thromboendarterectomy and resections and replacement of long occluded femoral arterial segments have already been documented.[6,7] On the other hand, Cannon and Barker[8] have reported encouraging results in twenty out of twenty-three patients with extensive femoral occlusions after thromboendarterectomy, in instances where the popliteal and more distal vessels were patent. Warren,[9] using the same technique, however, was disappointed with the results in this type of lesion.

Although restoration of continuity of blood flow, using a vein graft, is not new,[10] it had certainly not been tried extensively until the report of Kunlin of Paris, in 1951.[11] We successfully used a saphenous vein to by-pass an aortic aneurysm in 1951, that had been wired previously (Fig. 1). This remained open until the patient's death, at approximately eighteen months postoperatively, which presumably resulted from a rupture of his abdominal aneurysm.

The early report of Julian, et al,[6] of femoral artery replacements using veins, was encouraging and the later reports of more extensive work using arterial homografts, both as direct grafts and by-passes (as in the series reported by Crawford, et al,[12]) have made the restoration of continuity of flow a practical reality. It has also been learned from experience to date, that a prime factor in the success of either endarterectomy or grafting is the presence of an adequate patent peripheral arterial tree or "run off."

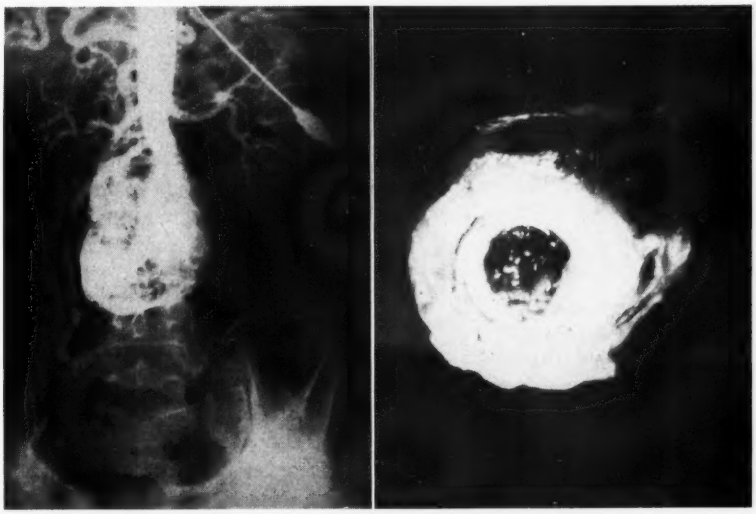


Fig. 1. *(left)* Aortogram in a forty-two-year-old white man made nine months after wiring procedure and aortoiliac shunt with an autogenous saphenous vein.

Fig. 2. *(right)* Thrombosed ilio-femoral Ivalon prosthesis removed two years after implantation for ruptured aneurysm of the common femoral artery. Microscopic section of this vessel showed marked proliferative connective tissue reaction with no signs of fibroblastic ingrowth.

The short supply of prepared or fresh arterial homografts stimulated the search for other prosthetics. Of the various materials being used at the present time, our own experiences, aside from the use of veins, has been mainly with the use of Ivalon compressed sponge, originally recommended as vascular prostheses by Shumway and his co-workers[13] and the braided nylon tubes originally described by Edwards and Tapp.[14]

Experiences in the Surgical Management of Obliterative Arterial Lesions in the Lower Extremity

Thromboendarterectory.—Using direct exposure and multiple extensive longitudinal arteriotomies, as described by Dos Santos[15], thromboendarterectomies were performed in three femoral arteries, from external iliac to popliteal level. One patient expired on the tenth postoperative day of a myocardial infarction, after extensive hemorrhage from the operative site and in one patient the entire area thrombosed within a few days and required

TABLE I. ILIAC—FEMORAL ARTERIAL SHUNTS OR REPLACEMENTS
Results in 24 cases

Prosthesis	Number	Success	Failure
Autogenous saphenous vein	8 (2*)	7	1
Nylon (Edwards-Tapp)	5 (1*)	5	0
Ivalon	11 (3*)	5	6 (3*)
Total	24 (6*)	17	7

*Replacements

TABLE II. FEMORAL—POPLITEAL ARTERIAL SHUNTS OR REPLACEMENTS
Results in 73 cases

Prosthesis	Number	Success	Failure	Expired
Saphenous vein	37 (1*)	29 (5-24 Mos.)	8 (1*)	
Nylon (Edwards-Tapp)	32	16 (3-12 Mos.)	13	3
Ivalon	4	0	4 (1 Mo.)	
Total	73	45	25	3

*Replacements

a mid-thigh amputation. The remaining patient had a good result with relief of claudication and has a persistent peripheral pulse after three years.

Short segment thromboendarterectomies were performed in five patients with acute arterial occlusions. Two of these were due to embolism and two to thrombosis. All were seen after twelve hours from the acute onset and three were at least twenty-four hours after the acute onset. One of the patients seen after twenty-four hours expired within twenty-four hours of surgery and was found to have multiple emboli in the renal, splenic and cerebral vessels. Another patient seen twenty-four hours after onset, required a saphenous vein graft of the common femoral artery, since the remaining vessel, in the site of the embolus, after endarterectomy was too friable to hold sutures. This patient is well, with good peripheral pulses, thirty months after surgery. The remaining three patients had patent vessels on follow-up examination, two at one year and one at three months.

Iliac Femoral Arterial Replacements and Shunts.—The results of our twenty-four iliac-femoral arterial shunts and replacements are summarized in Table I:

Of the eight instances in which an autogenous saphenous vein was used, there was one failure and this was in a shunt with poor distal "run-off" causing a thrombosis in the immediate postoperative period. The successful vein grafts have all existed over two years. The five Edwards-Tapp nylon tubes used at this level, have remained open for from three to twelve months. Tubes of 5/16 inch diameter were used in all instances.

Of the eleven compressed Ivalon prostheses used at this level, six failed. Three of these were direct replacements. One became thrombosed within the first twenty-four hours after surgery, one at three months and one after two years. Of the three shunts with Ivalon that failed, all were thrombosed within twenty-four hours of the surgery. The successful Ivalon grafts were all patent over fourteen months, at the last follow-up.

Of this latter group, only four patients had replacements for femoral aneurysms, all of which were either leaking or had ruptured.

Femoral Aneurysms.—A total of nine femoral aneurysms were seen in this series of patients. Two of these were ruptured arteriosclerotic lesions of the common femoral artery. When first seen, and were replaced by Ivalon prostheses. One of these became infected, thrombosed and was removed at two months. This patient expired and is included in Table II. The other became thrombosed at two years and was removed (Fig. 2). This was replaced by a braided nylon tube and is included as a successful graft in Table I.

Two traumatic aneurysms of the superficial femoral artery, were replaced by Ivalon prostheses and both failed, due to hemorrhage, secondary to postoperative heparinization and had to be removed. Both limbs survived with functional ischemia. These are included as failures in Table II.

Four other aneurysm lesions of the superficial femoral artery were treated by lumbar sympathectomy, alone, and one by wrapping with Ivalon. All were free of symptoms from either embolism or thrombosis after three years.

Femoral-Popliteal Arterial Shunts.—Table II summarizes the results in this group of seventy-three instances of surgery.

Twenty-nine out of thirty-seven saphenous, autogenous and homogenous venous shunts or replacements were open at follow-up examination, five to twenty-four months after surgery.

In one instance, an autogenous vein was used to bridge a traumatic occlusion. This thrombosed within a few hours. In at least two instances, the shunts used were composed of both the patient's own saphenous vein and one or more segments of homogenous vein grafts.

Sixteen of thirty-two Edwards-Tapp nylon shunts were still open at from three to twelve months' follow-up examination. Thirteen of these shunts failed. Two of these failures were instances in which a prosthesis of ¼ inch diameter was used. An almost immediate thrombosis occurred in each instance. The remaining failures were associated with poor run-off and with thrombosis of the shunt within two months of the operative procedure.

In one case (mentioned above under Femoral Aneurysms), there was a frank infection along the course of the prosthesis and the patient succumbed to a septicemia. In two other cases, patients died in the immediate postoperative period of coronary arterial disease.

Compressed Ivalon prostheses were used in four instances and failed in all. In two patients, almost immediate thrombosis resulted and in two (mentioned above under Femoral Aneurysms), repeated hemorrhage through the graft, secondary to postoperative heparinization, necessitated finally, ligation of the femoral artery.

Popliteal Aneurysms.—In Table III, are summarized our results with twenty popliteal aneurysms.

Eleven popliteal enurysms were treated with lumbar sympathectomy. Eight out of these eleven were thrombosed at the first onset of symptoms. Of this group, four patients had repeated peripheral embolic episodes within one year. One of these produced gangrene and required amputation. One of the group ruptured and required subsequent resection. Three of these original eleven had subsequent resection of the aneurysm. One patient in whom a primary lumbar sympathectomy and resection of the aneurysm were done, died in the first week postoperative, of acute coronary insufficiency.

One patient was seen for the first time with a ruptured aneurysm and impending gangrene of the extremity. Because of his poor general condition, a simple resection of the aneurysm was done, yielding a good result—a usable extremity but with claudication.

In eight instances, primary resection with autogenous vein grafting was attempted, after sympathectomy. Four of these failed almost immediately, due to thrombosis and resulted in viable extremities but with claudication. Four were successful and have functionally good extremities without claudication.

TABLE III. SURGICAL TREATMENT OF POPLITEAL ANEURYSMS
Results in 20 cases

Treatment	No.	Success Functional	Claudication	Amputation	Expired
Lumbar sympathectomy	11		10	1	0
Sympathectomy & resection	(3)		(3)		(1)
Resection only	1		1		
Sympathectomy resection and vein replacement	8	4	4		
Total	20	4	15	1	(1)

Discussion

Encouraged by the experimental work of Shumway[13] and by our own successful use of compressed Ivalon sponge prostheses in the replacement of aortic lesions, we attempted its use at the iliac and femoral level. As had recently been documented experimentally by McCaughan[16] we found that replacement of vessels (with this material) having an inner diameter of 8 mm or less, would result in failure from early thrombosis in a high percentage of instances. We now have begun to see late failures from thrombosis of iliac and femoral Ivalon prostheses. As can be seen in Figure 2, there is a great deal of reaction surrounding this material, making it a thick, firm tube in contrast to the pliable and elastic one that was originally inserted. This makes accommodation to motion practically impossible.

With motion, as in the hip joint, the host vessel may become occluded by folding against the end of this mass and this cause occlusion and subsequent thrombosis. This may have been the mechanism of occlusion of the graft shown in Figure 2. In view of these experiences, we have abandoned the use of compressed Ivalon tube prostheses in areas distal to the common iliac or similar-sized vessels where motion may be a problem.

It seems best to leave a patient with his own blood vessels, if they can be repaired and will heal to a reasonably good state of function. Thromboendartectomy, therefore, seems to be a procedure of choice.

In spite of the fact that we have not used it extensively, we are interested in the further developments of the method which might give more promise of a lasting functional result.

For short segments and especially in instances of acute occlusion, either by embolism or spontaneous thrombosis in severely sclerotic femoral

arteries, we feel that endarterectomy is definitely necessary for a successful result.

Our experience with the treatment of long-segment femoral arterial occlusions has shown the by-pass technique (using autogenous saphenous vein or crimped braided nylon tubes—Tapp-Edwards, 5/16 inch diameter) to be most successful. However, the follow-up of patients, in whom saphenous veins have been used, is only a little over two years and those in whom braided nylon tubes have been used, only one year. This limits our drawing any final conclusions on the relative merits of each method.

The most satisfactory handling of the symptomatic or asymptomatic popliteal eneurysm, appears to be sympathectomy followed by immediate resection. Since the incidence of functional ischemia (intermittent claudication) is so great in these patients, an attempt at restoration of continuity of blood flow should be made using either an autogenous vein or crimped nylon prosthesis and employing an end-to-side technique for the distal anastomosis.

The most satisfactory distal vascular anastomosis in arteriosclerotic occlusive disease, at this time, appears to be that made with a by-pass, end-to-side technique into the proximal popliteal artery, as described by Linton.[7] However, the technique of McAllister[17]—that of leaving the diseased vessel in place and making an end-to-end distal anastomosis is worthy of further trial. In the replacement of popliteal aneurysms we have had only four out of eight successful procedures with autogenous veins using the end-to-side technique. Not only does the diseased condition of the distal vessels affect the end results here but also implicated is the small calibre of the vessels involved. The problem at this level is similar to that encountered in the surgical approach to coronary artery disease. It seems that for vessels of such small calibre, replacement is almost a practical impossibility but some types of thromboendarterectomy, such as by hydraulic dissection instead of mechanical dissection, may hold more promise.

We believe that for successful vascular reconstructions, certain of the principles stated by Linton[7] should be adhered to, namely:

1. A suitable graft must be available.
2. The site of proximal anastomosis must be high enough in the patient's arterial system to supply an ample volume of blood at an effective pressure.
3. There must be an adequate distal "run-off."
4. An arteriogram should be made pre-operatively to determine if the above conditions (2 and 3) are satisfied.
5. Meticulous technique should be used and excessive trauma avoided.
6. Dilute Heparin should be used in occluded distal vessels and in the operative site—(0.02 per cent) solution during anastomosis but not post-operatively.
7. Most rigid asepsis should be practiced.

Summary

The results of experiences are presented in twenty-four iliac-femoral arterial shunts or replacements and seventy-three femoral-popliteal arterial shunts or replacements using autogenous and homogenous veins, braided nylon (Edwards-Tapp) tubes and compressed Ivalon tubes. The results of our experiences in treating twenty popliteal and femoral aneurysms is also presented.

The limited experience in our use of thromboendarterectomy is also discussed.

Our most satisfactory results, for long segmental occlusions in the iliac-femoral and femoral-popliteal areas, have been with the use of autogenous saphenous veins and braided nylon tubes, both as shunts and as replacements.

Sympathectomy and resection of popliteal aneurysms has been the most satisfactory in this group of cases. The further attempts at replacement with autogenous veins, after resection of popliteal aneurysms, is described in eight cases with encouraging results in one half of these.

References

1. Gifford. R. W., Jr., Hines, E. A., Jr., and Janes, J. M.: An analysis and follow-up study of 100 popliteal aneurysms. Surgery, 33:284-293, 1953.
2. Matas, R.: Endo-aneurysmorrhaphy. Surg. Gynec. & Obst., 30:456-459, 1920.
3. Lilly, G. D.: The management of aneurysms of the lower extremities. Ann. Surg., 123:601-605, 1946.
4. Linton, R. R.: The arteriosclerotic aneurysm. Surgery, 26:41-58, 1949
5. Julian, P. C., Dye, W. S., Javid, H., and Gove, W. J.: The use of vessel grafts in the treatment of popliteal aneurysms. Surgery, 38:970-980, 1955.
6. Julian, O. C., Dye, W. S., Olwin, J. H., and Jordan, P. H.: Direct surgery of arteriosclerosis. Ann. Surg, 36:459-474, 1952.
7. Linton, R. R.: Some practical considerations in the surgery of blood vessel grafts. Surgery, 38:817-834, 1955.
8. Cannon, J. A., and Barker, W. F.: A successful management of obstructive femoral arteriosclerosis by endoarterectomy. Surgery, 38:48-60, 1955.
9. Warren, R.: Evaluation of thromboendarterectomy for arteriosclerosis obliterans of the femoral artery. Surg. Gynec. & Obst., 104:571-578, 1957.

(Continued on Page 334)

Surgical Considerations in the Management of Cerebrovascular Disease

E. S. GURDJIAN, M.D., J. E. WEBSTER, M.D.,
W. G. HARDY, M.D., D. LINDNER, M.D.
Detroit, Michigan

AMONG 200 patients entering the hospital with a diagnosis of "stroke," occlusive disease was present in a little over half of the cases (Table I). In Table II are tabulated the patients with the provisional diagnosis of stroke, who proved to have surgical mass lesions. About 10 per cent of the group of 200 patients, therefore, had mass lesions needing surgical intervention. Massive hematomas are not very common among this group. In Table III are shown the diagnoses, after careful study, of certain cases with the initial provisional diagnosis of stroke.

In many instances, as seen in Table I, the pathologic disease associated with a stroke syndrome is in the neck or at the base of the brain with occlusion of the carotid or vertebral complex and the larger vessels of the circle of Willis.

Carotid artery thrombosis in the neck may be complete or partial. The occlusion may begin at the bifurcation and extend up toward the siphon, or there may be a retrograde thrombosis with the initial thrombotic involvement at the siphon. However, the greatest majority are examples of thrombosis at the bifurcation in the neck due to atheromatous changes. A complete occlusion may be fresh or chronic. In some instances an occlusion of the internal carotid artery may occur with few symptoms and signs and the disease process may be found in the routine study of the patient.

Among a little over 100 cases of complete occlusion of the internal carotid artery in the neck, a hemiplegia or hemiparesis was present in 90 per cent; there was a history of a single involvement in 70 per cent of this group; and among 30 per cent, there were multiple episodes of weakness or paralysis. The time of onset of the weakness or paralysis was during rest or in bed in 20 per cent, and during activity or daytime in about 80 per cent. The onset was abrupt in about 80 per cent.

TABLE I. OCCLUSIVE DISEASE

Carotid artery (complete)	21
Carotid artery (partial)	20
Anterior cerebral	15
Basilar artery (partial)	15
Middle cerebral trunk	9
Basilar artery (complete)	5
Post. cerebral artery occlusion	2
Arteriolar disease	32

TABLE II. SURGICAL MASS LESION

Brain tumor	16
Intracerebral hematoma	5
Subdural hematoma	3
Brain abscess	1

TABLE III. OTHERS

Embolism	11
Cerebral hemorrhage (hemorrhagic infarction)	8
Cerebrovascular insufficiency	9
Saccular aneurysm (1 A/V)	4
Cerebral atrophy	2
Post ictal state	1
Syphilis	1
Encephalitis	4
Miscellaneous	16

Unconsciousness and coma was noted in 20 per cent. Generalized or Jacksonian seizures occurred in 10 per cent; with the Jacksonian and the generalized seizures in equal numbers. Headache was present in one of four or five patients. Visual disturbances were noted in 10 per cent with homonomous hemianopic defects in half of the cases and a complete blindness of one eye in the other half. When there is unilateral blindness, the possibility of occlusion of the common, internal and external carotid arteries is much more likely.

With partial occlusions due to atheromatous plaques, the symptomatology has involved episodic

From Wayne State University Neurosurgical Service, The Grace and Memorial Hospitals, Detroit, Michigan.

The work discussed in this paper has been aided by the Kresge Foundation.

Presented at the Symposium on Peripheral Vascular Disease co-sponsored by the Minnesota Heart Association and the Mayo Foundation, Rochester, Minnesota, September 25, 1957.

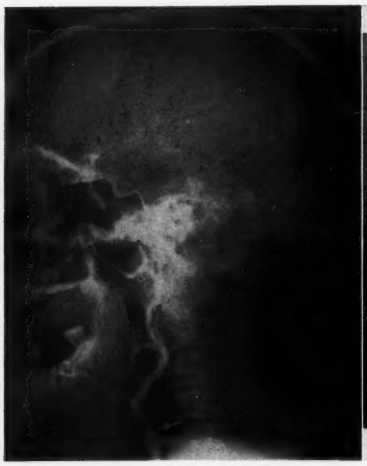


Fig. 1. Sudden onset of paralysis of the left half of the body with clear cerebrospinal fluid. Angiography showed complete occlusion of the internal carotid artery at the bifurcation. Arrows indicate excision of a portion of the internal carotid artery and cervical sympathectomy. Weakness of the left half of the body completely disappeared, patient (present age, seventy-three years) has been followed for two years with no evidence of recurrences, no anticoagulation used.

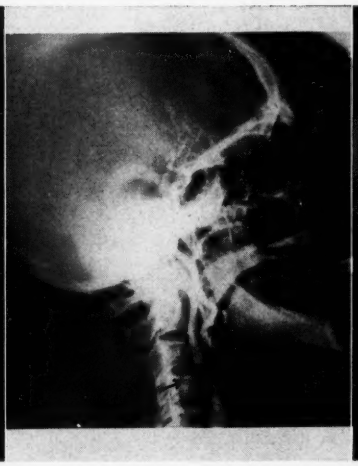


Fig. 2. Partial occlusion of the internal carotid artery at the bifurcation due to atheroma associated with repeated attacks of weakness of the left half of the body.

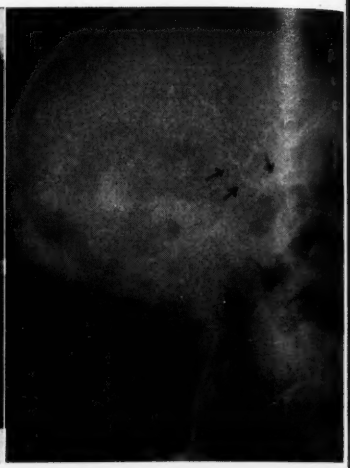


Fig. 3. Example of internal carotid artery thrombosis with visualization of a portion of the carotid siphon intracranially through collateral supply from frontal and ophthalmic vessels. Arrows point to the internal carotid siphon and the ophthalmic artery. External carotid appears to contribute significantly to the internal carotid circulation through intercommunications.

complaints of weakness or numbness in one-half or a portion of one-half of the body. In an occasional case, a more enduring weakness or paralysis has been seen. In angiograms obtained to include the carotid bifurcation, partial occlusion of the internal carotid artery is a common finding (10 per cent) among patients with "stroke" syndrome. The patients with partial occlusion may be helped by medical and/or surgical management.

Since, in many instances, atheromatous plaques may precede the eventual occlusion of the carotid bifurcation, the possibility of early diagnosis and surgical or medical management to prevent an on-coming complete occlusion must be considered.

Surgical treatment will depend upon the pathologic state revealed by angiography and exploration of the carotid artery. The cases may be divided into the following types:

1. An acute fresh occlusion in which a thrombectomy may be followed by re-establishment of the blood flow.

2. A chronic occlusion in which excision of a portion of the carotid artery and a servical sympathectomy may be of some value. It is now apparent that the external carotid circulation contributes significantly to the internal carotid circulation in cases in which the internal carotid in the neck is thrombosed. The use of sympathectomy to enhance the circulation by vasodilation of the extra-cranial vessels may be of value. Among the 25 per cent of the patients who appear to recover completely following a chronic occlusion of the internal carotid artery, the external carotid's contribution to the cerebral circulation is undoubtedly a factor.

3. A partial occlusion (and occasionally in chronic, and apparently complete occlusion) in which intimectomy may re-establish the blood flow.

Among fifty-five patients in our group, the neck was explored. In all but five, there was a chronic complete occlusion of the internal carotid. Among the five with acute occlusions, only three bled from the distal end of the artery after removal of the clot. Although the circulation was re-established acutely, postoperative angiograms performed several weeks later, revealed that in two cases, clotting had reoccurred with complete occlusion of the vessel.

When there is good bleeding from the distal end of the carotid artery and when the bifurcation

is occluded by atheromatous disease, several methods of management are possible: (1) an external carotid artery shunt to the distal end of the internal carotid; (2) the use of an inanimate tube for end to end or side to end anastomosis; (3) the use of a homologous graft, and (4) intimectomy.

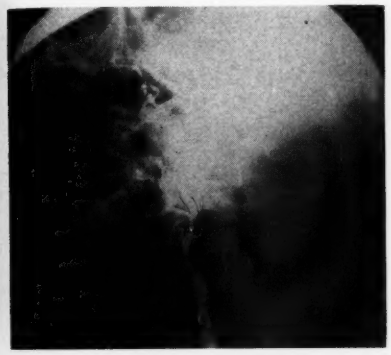


Fig. 4. A man aged sixty-three, seen six months after onset of right hemiparesis and aphasia. Angiogram revealed thrombosis of the internal carotid artery. Follow-up for two years with no improvement in the aphasia, some improvement in the weakness of the right half of the body. No operative intervention performed in this case.

Grafting of the external carotid artery to the patent internal carotid is not desirable in the authors' judgement because this destroys a good source of collateral circulation to the internal carotid through the frontal and ophthalmic arteries. The use of an end-to-end anastomosis of the common carotid to the patent internal carotid is mechanically impossible in many instances because of insufficient length. The use of end-to-end or side-to-side homografts has been satisfactory in the peripheral circulation, particularly in the lower extremities. In our hands, this method has not been satisfactory, thus far, thrombosis occurring rather rapidly due most probably to the small caliber of the internal carotid artery.

Crimped nylon grafts were investigated by trials within the aortas of dogs; this vessel is larger in size than the internal carotid artery in the adult human. In twenty-eight experiments it was found that in four cases the lumen of the tube was patent for one to three months, but in six instances, complete occlusion occurred from an intimal growth in three to seven months. Use of an inanimate tube for vessels of the size of the internal carotid artery may not be satisfactory for long periods. This is not to say that such tubes are not desirable or even ideal if the lumina remain patent indefinitely or if the temporary patency will allow sufficient time for collateral circulation to develop. More work should be done for the purpose of obtaining the best material for grafting. We have not employed nylon tubes in the human carotid thus far. In three dogs, the intima of the descending aorta was excised with the electrocautery current. The aneurysmal-like dilatation of the vessel did not progress. Later, the local dilatation became reinforced by connective tissue, the lumen of the vessel remained smooth-lined and patent.

Fig. 5. A side-to-end human homograft which was found to be occluded.

In patients having partial occlusions of the carotid bifurcation, with symptoms of cerebrovascular insufficiency, excision of the atheromatous plaque has been attempted in seven instances. In order to establish the fact that the cerebral circulation is insufficient because of the presence of this stenosis, compression of the opposite carotid should result in dizziness or syncope in ten to fifteen seconds. It is also important to compress the affected vessel to see whether or not complete

occlusion will result in increasing the symptoms or signs. This will help evaluate the extent of the insufficiency and may demonstrate any untoward effects from the complete temporary occlu-

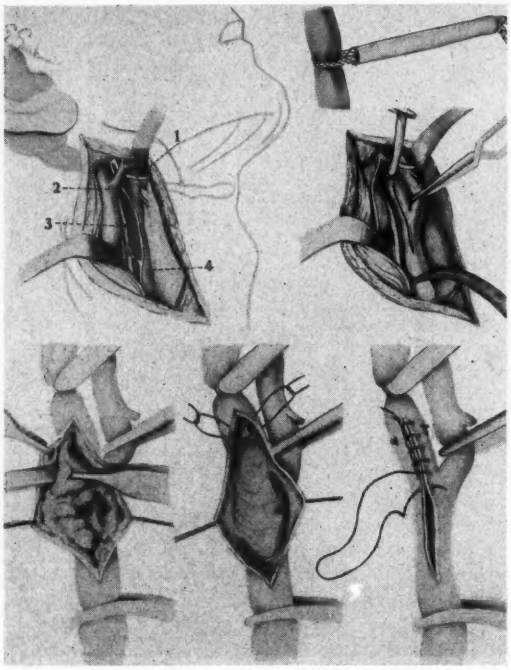


Fig. 6. Technique of intimectomy is illustrated.

sion of the stenosed vessel during the operation, or postoperatively by thrombosis. Compression of the carotid artery on the side of the stenosis in the seven cases above alluded to, did not result in any untoward effects. If compression for ten to twelve minutes causes increased weakness of the opposite half of the body from the partially occluded side, then intermittent carotid compression for a period of several days may result in an improvement in this state. If not, such a patient should be operated under hypothermic conditions to minimize the effects of the ischemia of the brain. The acutely paralyzed patient who shows an occluded carotid in an emergency angiographic study should probably be operated under hypothermic conditions.

Under intratracheal anesthesia, the carotid bulb area and the internal and external carotid arteries are exposed. The deep facial vein emptying into the internal jugular is doubly ligated and cut in order to give as much exposure superiorally under the lower jaw as possible. The twelfth cranial nerve can be retracted superiorally, giving a little more room in exposing the internal carotid artery in this area. In some instances it is conceivable that the twelfth cranial nerve may have

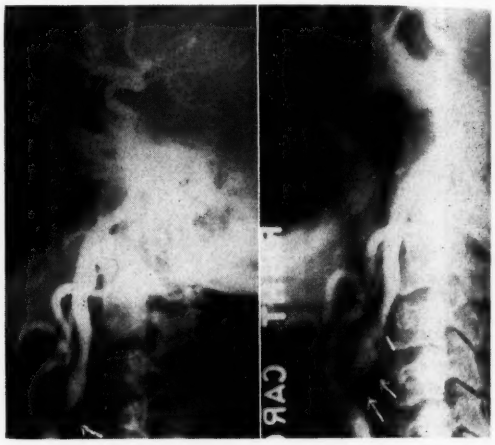


Fig. 7. *(Left)* Angiogram before intimectomy showing a marked stenosis of the internal carotid artery at the bifurcation. *(Right)* Angiogram eleven weeks after intimectomy showing patent internal carotid artery which now does not show the stenosis.

to be sectioned, although this has not been necessary in our cases. If section is done, then a suture of the nerve afterward, before closure of the wound is of course indicated. Branches of the ansa hypoglossi usually are sacrificed. The adventitia of the carotid bifurcation and the internal carotid artery is not disturbed in order that this layer be available for suture closure of the incision in the wall after excision of the atheromatous intimal layer. The vagus nerve is identified and exposed.

Suitable arterial clamps are used to occlude the proximal and the distal portion of the vessels. In order to occlude the distal portion of the internal carotid artery, a Number-4 braided silk or a tape may be placed around the artery, then passed through a section of polyethylene tubing to form a loop, then tightened about the vessel. This provides more room for working. For occlusion of the common and external carotid arteries, we use long handled bent clamps so that they lie outside the field of operation. If a hypersensitive carotid sinus reflex is present, xylocaine solution is infiltrated about the bulb before any manipulations are begun. Also, 1/50th to 1/100th grain of atropine sulfate is used intramuscularly or intravenously to protect such a patient. We

have not used pumping of blood from the common carotid to the internal carotid (distal to the clamps) due to the restricted flow which existed pre-operatively.

syndrome. Massive intracerebral hematomas may be readily diagnosed by angiographic studies. Such an example is shown in Figure 8. In this patient a 40-gram clot was removed with excellent clinical

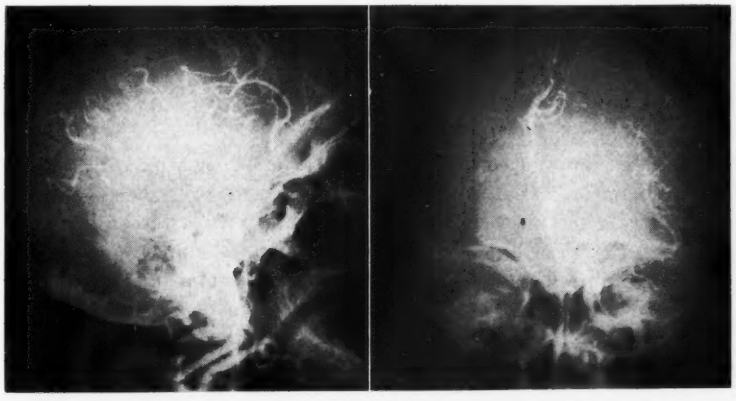


Fig. 8. Carotid angiogram showing left parietal intracerebral mass which proved to be a large intracerebral hematoma. This patient's right-sided paralysis and aphasia completely disappeared within two months after removal of the clot.

Through a linear incision the area of stenosis is exposed; a plane of cleavage is readily identified and the stenotic material internal to the lamina of the internal elastic membrane is removed. The area is flushed with saline and heparin solution and horizontal mattress stitches of 04 waxed arterial suture are used for closing the incision. Air and other matter are permitted to escape out of the vessel before completing closure. In instances where the atheromatous intima is not restricted to the area of the excision, it may be important to suture the intima to the adventitia with several sutures to keep the intimal lining from being dissected by the flow of blood. A strip of gelfoam is held over the sutured vessel using temporary pressure with cottonoid. In a few minutes the incision becomes sealed.

If this method of management is impossible because of the extreme friability of the artery wall, then a homologous graft is suggested.

Before closing, a few words should be said concerning surgical hematomas causing the stroke

results, from the left parietal lobe immediately lateral to the ventricle. Although in many instances there may be extensive deficits in neural function, in a few, spectacular results may be obtained.

Conclusions

1. Evacuation of a massive intracerebral hematoma may be worthwhile.

2. In complete and chronic occlusions of the internal carotid artery, excision of a portion of the vessel and cervical sympathectomy may be valuable.

3. In partial occlusions at the carotid bifurcation, intimectomy in many cases can re-establish the blood flow. Extreme caution should be exercised in evaluating the results.

4. The mechanical removal of occlusive atheromatous formations to maintain the cerebral circulation and to delay cerebrovascular failure must be considered until atheromatous disease of vessels can be prevented or ameliorated by other means.

Surgical Treatment of Aneurysms and Occlusive Disease of the Abdominal Aorta

DWIGHT C. McGOON, M.D.
Rochester, Minnesota

SIR ASTLEY COOPER introduced the surgical treatment of abdominal aneurysms when he first performed ligation of the abdominal aorta for an aneurysm in 1817, but little progress was made for many years thereafter. Although advances of a practical nature have been made only relatively recently, the underlying principles of these advances were considered and were rather well developed by experimental workers and applied by a few surgeons near the turn of the century. The notion that segments of arteries could be excised and continuity restored by end-to-end anastomosis, or by the use of arterial grafts, was conceived more than fifty years ago.

Aneurysms of the Abdominal Aorta

The vast majority of abdominal aortic aneurysms occur secondary to ateriosclerotic changes in the wall of the aorta, which cause it to be weakened and permit gradual stretching of the wall and dilatation. In accordance with well-known physical laws, as the wall becomes dilated and gradually stretched, the tension placed on it by the pressure of the blood within becomes increasingly great. Thus, a vicious circle is set in motion that is often finally terminated only by sudden rupture of the aorta and rapid death. This unfavorable prognosis in patients with aortic aneurysms has long been recognized. The studies of Estes[1] indicate that approximately 80 per cent of patients with this disease do not survive for five years, death being due in the majority of patients to rupture of the aneurysm. Somewhat similar findings have been reported by other investigators. Many of those persons who do not die of their disease suffer from severe disability caused by pain in the abdomen and back.

From the Section of Surgery, Mayo Clinic, Rochester, Minnesota.
Presented at the Symposium on Peripheral Vascular Disease co-sponsored by the Minnesota Heart Association and the Mayo Foundation, Rochester, Minnesota, September 25, 1957.

The great majority of abdominal aortic aneurysms arise below the level of the renal arteries. In a recent study reported by my colleagues, Ellis and associates,[2] only 7 per cent of 133 patients operated on at the Mayo Clinic showed involvement of the renal arteries by the aneurysm. It is not possible, however, to determine by physical examination the upper limits of the aneurysm. The aneurysmal sac itself may bulge superiorly from its site of origin and may come to overlap the relatively normal aorta at the level of the origin of the renal vessels. Only by dissection around the superior limit of the aneurysmal sac can the level of its origin be determined. The aneurysms are usually fusiform and may or may not have extensive adhesions and inflammatory reaction about them. Their lower limit may be just above the bifurcation of the aorta, or they may extend to the bifurcation, causing considerable tortuosity of the iliac vessels, or may extend inferiorly to involve the iliac vessels themselves.

As a result, perhaps, of stagnation of blood within the dilated aneurysmal sac in association with calcific and atheromatous changes, a laminated thrombus forms on the inner surface of the aneurysm. The laminated thrombus that lies immediately adjacent to the peripheral wall of the aneurysm gradually undergoes liquefaction necrosis, and at operation one commonly liberates large quantities of gray, oily, liquid material from the aneurysmal wall. This liquefaction necrosis of the thrombotic material supporting and lining the aneurysmal wall is considered an important factor contributing to eventual rupture of the aneurysm.

The clinical manifestations in this disease are characterized by a pulsating mass in the abdomen, accompanied by pain in the upper portion of the abdomen, lower part of the back and the lower extremities. The physical examination is especially important in diagnosis. The mass usually can be

palpated in the midabdomen at or slightly above the umbilicus, and it often extends more to the left of the midline than to the right. Anteroposterior and lateral roentgenograms of the abdomen usually demonstrate a rim of calcium that is pathognomonic of abdominal aortic aneurysm. Although aortography does have a role in the diagnosis of abdominal aortic aneurysms, it is unnecessary in most cases. Only in extremely doubtful situations, as with obese patients, is such a study indicated.

All patients who have aneurysms of the abdominal aorta should be seriously considered as candidates for operation. Patients who have severe coronary arterial disease may be advised not to undergo operation. Other serious diseases carrying a worse prognosis than that of an abdominal aortic aneurysm may be present and contraindicate surgical intervention. Evidence of leakage from the aneurysm constitutes an urgent indication for operation, although the risk of surgical treatment under these circumstances may be considerably increased. Age, alone, is no contraindication to operation but is of importance, in that persons of the older age groups who have small asymptomatic aneurysms should be less favorable candidates for operation.

The technique of the operation itself is largely standardized. A long midline abdominal incision is made, extending from the symphysis pubis below up to and along side the xiphoid process above, skirting the umbilicus to its left. By eviscerating the small intestine and placing it in a Lahey type of bag on the lateral abdominal wall, excellent exposure of the operative field is obtained. The transverse colon is reflected superiorly, and the terminal portion of the duodenum and the proximal portion of the jejunum in the region of the ligament of Treitz are mobilized to the right. An incision is made in the posterior peritoneum, thus exposing the aneurysm itself. The proximal segment of aorta is dissected free just below the level of the left renal vein, and a tape is placed about the aorta at this point. Similar tapes are placed about each common iliac artery below and the dissection is continued along the lateral margins of the abdominal aneurysm, with ligation of the inferior mesenteric artery. The mobilization of the aneurysm from the underlying spinal column and the lumbar vessels is accomplished only after the aorta is divided above and reflected inferiorly. Special care must be exercised to protect the iliac veins as they pass beneath the bifurcation of the aorta. Following removal of the aneurysm, reconstruction of the aorta must be accomplished. This may be done by utilizing a homograft of abdominal aorta, including the bifurcation; however, particularly when the proximal aorta is dilated, it may be advantageous to use a homograft of thoracic aorta, creating an end-to-end anastomosis above and an end-to-end anastomosis to one of the iliac vessels below. The other iliac vessel is anastomosed end to side.

A transition perhaps is occurring from the widespread use of homografts to the more common use of prosthetic grafts. The experience at the clinic to date with the Edwards-Tapp prosthesis has been most encouraging, and it or a similar prosthesis probably will find wider and wider application.

The afore-mentioned report of the results of surgical treatment of abdominal aortic aneurysms at the clinic included data on 133 patients undergoing operation; at exploration, the condition in ten of these was considered to be inoperable because of involvement of the renal arteries. A mortality rate of 13 per cent was experienced in 103 operations in which an aortic homograft was used. A mortality rate of 35 per cent occurred among patients undergoing emergency operation because of a ruptured aortic aneurysm. Six patients for whom homografts were employed died of postoperative hemorrhage. In one of these patients, the source of bleeding could not be found. Hemorrhage occurred from the suture line in four patients, and there was frank failure of the graft, with rupture through its midportion on the eighth postoperative day, in one instance. Similar experience in other reported series of cases suggests that perhaps tissue incompatibility may be an etiologic factor in the failure of grafts in these patients. As regards the long-term results of the treatment of abdominal aortic aneurysms, Dr. Lincoln Sheranian, a fellow of the Mayo Foundation, recently reviewed these statistics and has shown that the long-term outcome is exceedingly favorable.

Chronic Occlusive Disease of the Abdominal Aorta

Chronic occlusive disease of the terminal portion of the aorta or the iliac arteries is closely akin to abdominal aortic aneurysms as regards the etiologic factors. However, the formation of thrombi occurs initially in occlusive disease. The vessels

become narrowed as the result of progressive atherosclerosis until a critical point is reached and final obliteration by thrombotic material occurs.

Leriche[3] pointed out that clinical experience indicates that one may recognize this syndrome easily by three symptoms, namely: (1) absence of pulsation at the two femoral arteries, (2) noticeable blanching of the lower extremities on elevation and (3) inability of men to perform sexually. Perhaps even more characteristic than this so-called Leriche syndrome is the presence of slowly progressive distress in the calf, thigh, hip or back that is induced by activity and relieved by rest.

Of special emphasis in this disease is the fact that roentgenologic demonstration of the exact extent of the disease is indicated. The upper limit of the thrombosis and occlusion is nearly always sufficiently below the renal arteries to enable surgical relief, but knowledge of the lower limit of the occlusion and also the demonstration of the arterial tree of the leg are of fundamental importance with regard to the operative plan.

The surgical treatment of thrombotic occlusion of the terminal portion of the aorta is directed toward re-establishment of normal blood flow to the lower extremities. It may be unnecessary to resect that portion of the aorta involving the bifurcation, in which case a short segment graft is all that is required. In other instances, the lower anastomoses may be made through the common iliac artery on both sides or through its branches on one side. Becoming more and more widely accepted in the case of segmental arterial occlusion is the bypass type of graft utilizing an end-to-side anastomosis inferiorly, thus allowing both a larger anastomosis to be created and also preventing any diminution of collateral blood supply that may be present.

The results of operation for occlusive disease of the terminal part of the aorta or iliac arteries were reported from the clinic by Welch and coworkers.[4] A mortality rate of 4 per cent was encountered among the seventy-four patients who underwent resection and grafting; 69 per cent of the patients had excellent results, 18 per cent had fair results and only 9 per cent showed no improvement. Failures in this series were considered to be due principally to a lack of appreciation early in the series for the necessity of carrying the resection distally until good vessels with good backflow were found, even though this necessitated separate incisions in the groin. Experience has emphasized the necessity of making the anastomosis to the common or superficial femoral artery if the vessels located farther cephalad are not satisfactory. This again serves to illustrate the importance of adequate arteriographic visualization of the vessels in the leg, for an anastomosis to the common iliac artery will fail in a high percentage of cases if the superficial femoral artery on the same side is occluded. Similarly, a graft with an anastomosis to the superficial or common femoral artery may fail if the vessels lower in the leg are occluded.

References

1. Estes, J. E.: Abdominal aortic aneurysm: Study of 102 cases. Circulation, 2:258-264 (Aug.) 1950.
2. Ellis, F. H., Jr., Kirklin, J. W., and Bernatz, P. E.: Aneurysms of the abdominal aorta. S. Clin. North America, August, 1957, pp. 1047-1057.
3. Leriche, René: Thrombotic obliteration of the bifurcation of the aorta. Read at the Halsted Centennial Celebrations at the Johns Hopkins Hospital, Baltimore, Maryland, February, 1952.
4. Welch, J. S., Kirklin, J. W., Ellis, F. H., Jr., and Bruwer, A. J.: Resection and grafting for chronic occlusion of the terminal aorta or iliac arteries. J.A.M.A., 164:1045-1049 (July 6) 1957.

SEGMENTAL OCCLUSION OF THE FEMORAL ARTERY

(Continued from Page 326)

10. Pringle, J. H.: Two cases of vein grafting for the maintenance of direct arterial circulation. Lancet, 1:1795-1796, 1913.
11. Kunlin, J.: Le traitement de l'ischemic arterique par le greffes veineuse longue. Rev. Chir., Paris 1951, 70:206.
12. Crawford, E. S., Creech, O. Jr., Cooley, D. A., and De Bakey, M. E.: Treatment of arteriosclerotic occlusive disease of the lower extremities by excision and graft replacement or by-pass.
13. Shumway, N. E., Gliedman, M. D., and Lewis, F. J.: An experimental study of the use of polyvinyl sponge for aortic grafts. Surg. Gynec. & Obst., 100: 703-706, 1955.
14. Edwards, W. S., and Tapp, J. S.: Peripheral artery replacement with chemically treated nylon tubes. Surg. Gynec. & Obst., 102:443-449, 1956.
15. Dos Santos, J. C.: Sur la desobstruction des thromboses arterielles anciennes. Mem. Acad. chir., 73: 409-411, 1947.
16. McCaughan, J. J. Jr.: The experimental use of Ivalon arterial grafts. Surgery, 42:717-721, 1957.
17. McAllister, F.: Experiences with replacement of segments of diseased femoral and popliteal arteries. Surgery, 38:964-969, 1955.

Aneurysms of the Thoracic Aorta

F. HENRY ELLIS, JR., M.D.
Rochester, Minnesota

IT IS now well recognized that aneurysms of the aorta, whatever their location, pose a serious threat to life. The development of disabling symptoms and the probability of ultimate rupture are well known. The life expectancy for patients with syphilitic aneurysms of the thoracic aorta has been estimated to be six to nine months.[1] Similar statistics for thoracic aneurysms of other varieties are not available but it is likely that thoracic aneurysms of arteriosclerotic, traumatic or congenital origin also carry a poor prognosis.

Although surgical treatment of a thoracic aortic aneurysm was undertaken more than fifty years ago,[2] this approach has been revived only recently.[3] Probably the most significant stimulus to the development of aortic resectional surgery has been the introduction of the clinical use of aortic homografts by Gross and associates[4] and, more recently, the development of suitable prosthetic materials.[5] Experience with the treatment of thoracic aortic aneurysms at the Mayo Clinic dates back to January, 1954, and forms the basis for this report.

Types of Aneurysms

Twenty-four patients with this disease have been treated. Their ages ranged from five to seventy-three years. Almost two thirds of them were in the sixth, seventh and eighth decades of life.

A wide variety of aneurysms are represented in this relatively small group of patients (Table I). Unlike most reported series, in which syphilitic aneurysms predominate, arteriosclerotic aneurysms were the most common. As the over-all age of the general population increases, it appears likely that an even greater proportion of arteriosclerotic aneurysms will be encountered. They are usually fusiform in shape and more often involve the distal part of the aortic arch and the descending aorta than they do the proximal portions of the aorta. Ten patients had aneurysms of this type (Fig. 1 and 2).

There were five syphilitic aneurysms in this group of patients. Classically, aneurysms of this type occur in the ascending aorta and the aortic arch. Although they are often saccular and have a narrow mouth suitable for lateral excision and aortorrhaphy, these characteristics were not present in any of these five patients.

TABLE I. TYPE OF THORACIC AORTIC ANEURYSMS: 24 Surgical Cases

Type	Cases
Arteriosclerotic	10
Syphilitic	5
Traumatic	4
Congenital	2
Mycotic	2
Dissecting	1
Total	24

Traumatic aneurysms were noted in four patients. Aneurysms of this type are located most commonly in the descending thoracic aorta just distal to the origin of the left subclavian artery at the site of the ligamentum arteriosum. Another common site is the ascending aorta just distal to the aortic valve. Both these sites are relatively fixed points and are placed under stress during rapid deceleration. As the number of automobile and airplane accidents increase, such aneurysms will be seen and recognized with increasing frequency. The surgical results should prove to be good in patients with traumatic aneurysms. They are usually younger than patients with arteriosclerotic or syphilitic aneurysms and the adjacent aortic wall is usually of good quality.

Two patients had congenital aneurysms. These aneurysms are rare. They may be of the aortic-sinus type or they may arise in the region of the ligamentum arteriosum. Both patients had aneurysms of the latter variety.

Two patients had mycotic aneurysms; one occurred distal to a zone of coarctation and one

From the Section of Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

Presented at the Symposium on Peripheral Vascular Disease co-sponsored by the Minnesota Heart Association and the Mayo Foundation, Rochester, Minnesota, September 25, 1957.

occurred at the suture line following resection of a coarctation of the aorta and end-to-end anastomosis performed elsewhere (Fig. 3 and 4).

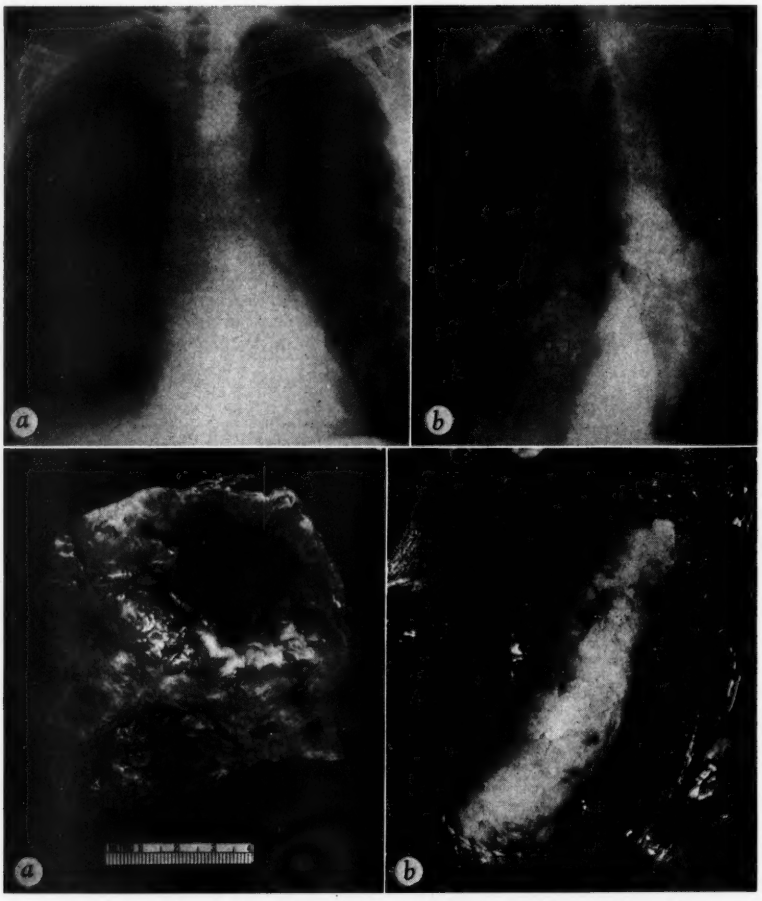


Fig. 1. Arteriosclerotic aneurysm of the descending thoracic aorta in a fifty-seven-year-old man. (a) Posteroanterior roentgenogram. (b) Left anterior oblique projection.

Fig. 2. (a) Opened aneurysmal sac after surgical excision in case illustrated in Fig. 1. (b) Homograft in place in same case.

The final patient had a dissecting aneurysm of the proximal portion of the descending aorta.

Operative Experience

Resectional operations for aneurysms located in the thoracic aorta pose certain problems not common to similar procedures carried out on the abdominal aorta. It is not feasible to place clamps across the thoracic aorta for long periods because of the danger of ischemic damage to the spinal cord. The safe period of aortic occlusion has been estimated to be fifteen to thirty minutes. The great variability in blood supply to the cord may make even briefer periods of occlusion risky. Therefore, various techniques have been employed to avoid this complication. Lateral excision and aortorrhaphy may be employed. This technique may be particularly suitable in the region of the ascending arch, since even brief periods of interruption of the circulation to the brain are not well tolerated. Excision of the aneurysm with insertion of a graft is, however, a preferable procedure, because aneurysmal recurrence at the suture line of the lateral aortorrhaphy was noted in the one patient treated in this manner at the clinic.

The use of temporary shunts to bypass the operative region allows continued circulation to

the body during resection. This method was used in one case and was found to have certain disadvantages. The operative procedure is necessarily prolonged and suture closure of the sites of connection of the temporary shunt may be difficult and dangerous, particularly if the entire aorta is diseased, as is often the case. Hemorrhage from one of these sites resulted in the death of one patient.

Hypothermia was employed in most of the remaining patients undergoing resection and grafting. By reduction of the arterial oxygen requirement of the central nervous system, a safe period of aortic occlusion up to one hour is permitted. Hypothermia is probably not necessary for lesions located below the eighth or ninth thoracic vertebra. A temperature of 32° C. is ideal and avoids some of the complications of hypothermia that occur at a lower temperature.

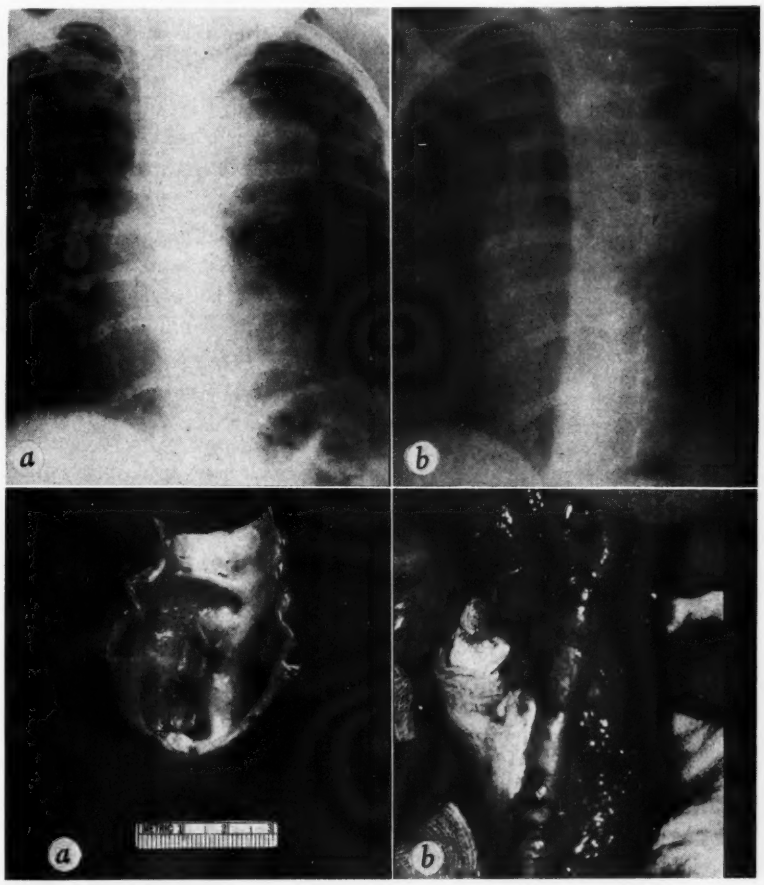


Fig. 3. Mycotic aneurysm in a six-year-old boy after resection of coarctation and end-to-end anastomosis. (a) Posteroanterior roentgenogram. (b) Left anterior oblique projection.

Fig. 4. (a) Opened aneurysmal sac in case pictured in Fig. 3. (b) Homograft in place in same case. (Figures 3a and 4 reproduced with permission of the publisher and authors from Martin, W. J., Kirklin, J. W. and DuShane, J. W.: Aortic aneurysm and aneurysmal endarteritis after resection for coarctation: Report of a case treated by resection and grafting. J.A.M.A., 160:871-874 [Mar. 10] 1956.)

Although hypothermia has been a great aid in operative procedures on the thoracic aorta, it has not solved all the problems. The increased work load imposed on the heart by high aortic occlusion can be of serious consequence. In an effort to overcome this, Cooley and associates[6] suggested the use of controlled extracorporeal circulation. By pumping blood from the left atrium to the lower part of the aorta via the femoral

artery, blood flow to the lower portion of the body is maintained during aortic excision and grafting.

Resection of the lesion was done on eighteen of these twenty-four patients with thoracic aortic aneurysms. The main cause of inoperability was the location of the aneurysm in either the ascending aorta or its proximal arch. A few instances of successful resection of aneurysms in this location with the aid of extracorporeal circulation have been reported.[7,8] The risks accompanying surgical intervention in this region, however, are obviously greater than when the more distal portions of the aorta are involved.

Grafts were used in seventeen of the eighteen patients on whom resection was done. As previously mentioned, lateral excision with aortorrhaphy was employed on one occasion. There were six deaths in this group of eighteen patients in the first weeks after operation. Hemorrhage, complications of hypothermia or both accounted for most of the deaths. In only one patient were neurologic signs and symptoms recognized in the postoperative period. This patient, operated on under hypothermia, underwent a prolonged period of aortic cross-clamping. Weakness of the lower legs developed, from which he has recovered almost completely. Three other patients died later, all as a result of hemorrhage; one had a ruptured recurrent thoracic aneurysm following lateral excision and aortorrhaphy and two bled because of complications related to the grafting procedure.

Homografts were used predominantly, fourteen patients being treated in such a fashion. An ivalon graft was employed in two patients and a crimped nylon tube in one. The choice of grafting material is controversial. It has been shown experimentally that there is a greater tendency for homografts to undergo degenerative changes when inserted into the thoracic aorta than when placed in the abdominal aorta.[9] For this reason prosthetic grafts may have certain advantages, although final proof is lacking. However, a greater tendency exists for bleeding to occur through the interstices of a prosthetic graft inserted into the thoracic aorta with the patient under hypothermia than when similar materials are used in the abdominal aorta under normothermic conditions.

Solutions unquestionably will be presented for many of the problems now connected with thoracic aortic surgery as understanding of these problems increases. In the foreseeable future, however, one will have to accept a higher mortality rate for resection of thoracic aortic aneurysms than for resection of aneurysms located in the abdominal aorta. Physicians must ask themselves if operations attended by a risk of this magnitude are justified. In view of the known poor prognosis of untreated aneurysms, surgeons are obligated, I believe, to undertake heroic measures for their correction.

Summary

Aneurysms of the thoracic aorta are a serious threat to health and life, and their surgical removal should be considered seriously.

A series of twenty-four operations for thoracic aortic aneurysms are reported. Arteriosclerotic aneurysms were the most commonly encountered. Resection was performed on eighteen patients, and grafts were employed in seventeen of these, homografts being used in fourteen patients, ivalon grafts in two and a nylon prosthesis in one.

Hypothermia was used as a means of avoiding ischemia of the spinal cord during cross-clamping of the aorta in most instances.

References

1. Kampmeier, R. H.: Saccular aneurysm of thoracic aorta: Clinical study of 633 cases. Ann. Int. Med., 12:624-651 (Nov.) 1938.
2. Tuffier, Th.: Intervention chirurgicale directe pour un a néurysme de la crosse de l'aorte: Ligature du sac. Presse méd., 1:267-271 (Mar. 19) 1902.
3. Cooley, D. A. and DeBakey, M. E.: Resection of the thoracic aorta with replacement by homograft for aneurysms and constrictive lesions. J. Thoracic Surg., 29:66-102 (Jan.) 1955.
4. Gross, R. E., Bill, A. H., Jr., and Peirce, E. C., II: Methods for preservation and transplantation of arterial grafts: Observations on arterial grafts in dogs: Report of transplantation of preserved arterial grafts in 9 human cases. Surg., Gynec. & Obst., 88:689-701 (June) 1949.
5. Edwards, W. S.: Plastic Arterial Grafts. Springfield, Illinois: Charles C Thomas, 1957, 126 pp.
6. Cooley, D. A., DeBakey, M. E. and Morris, G. C., Jr.: Controlled extracorporeal circulation in surgical treatment of aortic aneurysm. Ann. Surg., 146:473-485 (Sept.) 1957.
7. Cooley, D. A. and DeBakey, M. E.: Resection of entire ascending aorta in fusiform aneurysm using temporary cardiac bypass. J.A.M.A., 162:1158-1159 (Nov. 17) 1956.
8. DeBakey, M. E., Crawford, E. S., Cooley, D. A. and Morris, G. C., Jr.: Successful resection of fusiform aneurysm of aortic arch with replacement by homograft. Surg., Gynec. & Obst., 105:657-664 (Dec.) 1957.
9. Kanar, E. A., Nyhus, L. M., Schmitz, E. J., Sauvage, L. R., Moore, H. G., Jr., and Harkins, H. N.: Experimental vascular grafts. II. Some undesirable gross and microscopic changes observed in arterial homografts after implantation into the thoracic aorta of growing pigs: A preliminary report. Am. Surgeon, 19:915-923 (Oct.) 1953.

Effects of Irradiation of the Fetus

Ten-year Follow-up of Pelvimetry during Pregnancy

STEPHEN D. MILLS, M.D., ANDRE J. BRUWER, M.D.,
EDWARD A. BANNER, M.D., GEORGE D. DAVIS, M.D.,
ROBERT P. GAGE, M.S.
Rochester, Minnesota

AS WE advance into "the atomic age," we are becoming increasingly aware of the possible harmful effects of radiation energy on all living tissue. Especially sensitive to these effects are fetal tissue and the gonads. The public is besieged with implications of the dire results of undue exposure to ionizing radiation, the publicity being based chiefly on the measurable destruction at Nagasaki and Hiroshima where careful and accurate studies[1] have clearly documented in detail the harmful effects of atomic radiation on the population of those two cities.

The literature contains evidence of the unfavorable results of exposure to ionizing radiation[2] in the production of cancer of the thyroid gland or leukemia in patients who, as children, received x-ray treatment of an enlarged thymus gland. The increased incidence of leukemia in roentgenologists[3] as compared with the incidence in physicians not employing roentgen rays has been cited. There is evidence of an increased incidence of leukemia in British and Dutch patients with ankylosing spondylitis[4] treated repeatedly by irradiation. Stewart and co-workers[5] from England, in a recently reported study (in which an unusually large number of children were found to have leukemia or malignant disease following exposure to x-ray radiation during fetal life), have raised the question of the hazard of subjecting any pregnant mother to this exposure. At the 1957 meeting of the British Medical Association. Warrick[6] pointed out three kinds of potential danger to the fetus receiving roentgen radiation in the prenatal period: (1) occurrence of congenital deformities as a result of radiation injury during the first trimester, (2) damage to the gonads of mother and fetus resulting in gene mutations that might appear only in future generations and (3) the production of leukemia or malignant disease during the first 10 years of life from repeated small doses of irradiation. All of these disadvantages must be weighed against the value of information gained by obstetric radiology.

A study by the National Research Council[7] in 1956 of the biologic effects of atomic radiation suggested that the total man-made radiation to the gonads in an entire reproductive lifetime (birth to 30 years of age) should be kept less than 10 r to avoid harmful mutations of the genes. We are now receiving 3 to 4 r, on the average, from medical x-ray exposure, which is the same dose as unavoidable background radiation in a lifetime. The fall-out from the testing of atomic weapons is minimal, probably less than 0.5 r. The effect on all of us of the output of atomic energy plants is a matter of conjecture. A total dose of 200 r in a lifetime may be harmless if distributed over the years with a weekly dose of less than 0.3 r, according to Witts.[8] The average pelvimetric x-ray examination delivers a dose of 2.5 r to the fetus, according to Rabinowitch.[9] This is a dose in the range that may be harmful to the fetus and maternal gonads.

The previously mentioned report of Stewart and colleagues,[5] made just a year ago, has caused much concern to all confronted with this problem. In a survey of 1,500 children dying of leukemia or malignant disease before the age of ten years in the period 1953 to 1955, they found in the first 500 cases eighty-five children whose mothers had had x-ray exposure of the abdomen during the antenatal lives of these children, as compared to 45 children in a control group. This evidence suggested to Stewart and co-workers that children who receive x-ray irradiation before birth are

Read at the meeting of the Northwestern Pediatric Society, Bayport, Minnesota, September 27, 1957.

Dr. Mills is in the Section of Pediatrics, Drs. Bruwer and Davis are from the Section of Roentgenology, Dr. Banner is in the Section of Obstetrics and Gynecology and Mr. Gage is from the Section of Biometry and Medical Statistics, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

more prone to have leukemia or malignant disease subsequently than are those who have not been exposed to x-rays *in utero*. So challenging was this report that we were prompted to review our own experience in this connection, since it has been the practice of the Section of Obstetrics of the Mayo Clinic to use x-ray pelvimetry in many primigravidas to corroborate pelvic measurements. Pelvimetric x-ray examination may also be employed in multiparous patients having delivered elsewhere, who have delivered infants of less than average weight, or who give histories of dystocia possibly due to cephalopelvic disproportion.

The review of our own experience concerns 226 of 1,258 patients delivered in the hospital in 1946. These 226 patients had received x-ray pelvimetry during their pregnancies. This procedure had been carried out usually in the last trimester both to include those mothers expected to deliver at term and also to avoid the greater danger of inducing congenital malformations that may be induced early in gestation. The dose of radiation delivered at the depth of the fetus by pelvimetry in 1946 was calculated as 3.5 r. As this is more than the dose previously mentioned as harmful to the fetus we would expect any damage to the fetus to be evident in a study of the subsequent course of these children. Of the 226 children represented by the study, we had a complete 10-year record on 155, in none of whom was there any evidence of malignant disease or leukemia. The abnormalities and deaths in the 155 are summarized in the table. Also in an additional thirty-five, followed for varying periods of less than ten years, we could find none with evidence of leukemia or malignant disease. The remaining thirty-six patients could not be traced following birth.

Although this sample is small, the ten-year follow-up of 155 of the total 226 children (almost 70 per cent) who received x-rays antenatally gives no evidence to support the suspicion of an increased incidence of leukemia or malignant disease in such patients as suggested by Stewart and coworkers. Had our patients followed the pattern suggested by the British authors, we might have found some evidence in a ten-year period among the 190 traced.

To obtain some perspective of the problem it might be well to state that the death rate from

TABLE I. ABNORMALITIES IN 155 CHILDREN TRACED FOR TEN YEARS AFTER ANTENATAL IRRADIATION
(Pelvimetry Done in 1946)

Abnormality	Patients
Stillborn	2
Birth injuries—died	2
Prematurity—died	1
Congenital deformities	3
Coxa vara	1
Deformity of cervical spine	1
Microcephaly	1
Congenital deafness	1
Congenital cataracts	1

cancer including leukemia for children less than fifteen years of age in the total registration area of the United States in the year 1952 was approximately ten per 100,000 population of that age period. Stated differently, there were slightly more than 3,600 deaths in children less than fifteen years of age in the entire United States from all kinds of malignant neoplasms and leukemia in the year 1952. Though the incidence of these conditions is relatively large in childhood, the actual number of patients who die of them is small considering the size of the population in which they occur. In view of this low incidence, it is not unexpected that a series such as ours, which comprised only a small number of patients, contained no cases of malignant diseases or leukemia.

Rabinowitch[9] refuted the implication of Stewart and colleagues that there is a positive correlation between roentgen irradiation given antenatally and the occurrence of leukemia and malignant disease in the children subjected to such irradiation. He checked the records of all children dying of leukemia in his hospital area from 1940 to 1955. There had been more than 4,000 roentgen examinations during pregnancy, about a third of which were pelvimetries. There were but six deaths from leukemia in the age group less than six years; none of these children had received antenatal roentgen irradiation. It will require further carefully controlled studies of large numbers of patients to settle this question.

Conclusions

1. The use of x-ray pelvimetry in the third trimester of pregnancy appears to have shown no tendency to cause malignant disease or leukemia as a result of radiation injury to the fetus.

2. The advantages of x-ray pelvimetry to the obstetrician would seem to justify the very limited risk of potential injury to the fetus that is entailed in the use of the procedure.

References

1. Neel, J. V. and Schull, W. J.: The effect of exposure to the atomic bombs on pregnancy termination in Hiroshima and Nagasaki. In: National Academy of Sciences, Publication 461. Washington, D. C.: National Research Council, 1956.
2. Simpson, C. L. and Hempelmann, L. H.: The association of tumors and roentgen-ray treatment of the thorax in infancy. Cancer, 10:42-56 (Jan.) 1957.
3. March, H. C.: Leukemia in radiologists in a 20-year period. Am. J. M. Sc., 220:282-286 (Sept.) 1950.
4. Court-Brown, W. M. and Doll, R.: Leukaemia and aplastic anaemia in patients irradiated for ankylosing spondylitis. Medical Research Council, Special Report Series, No. 295. London: Her Majesty's Stationery Office, 1957.
5. Stewart, Alice, Webb, Josefine, Giles, Dawn and Hewitt, David: Malignant disease in childhood and diagnostic irradiation *in utero*. Lancet, 2:447 (Sept. 1) 1956.
6. Warrick, C. K.: X-ray damage to the fetus. Med. Sc., 2:32-33 (Aug. 25) 1957.
7. The biologic effects of atomic radiation: Summary reports from a study. In: National Academy of Sciences, 108 pp. Washington, D. C.: National Research Council, 1956.
8. Witts, L. J.: Recent work on leukemia in man. Lancet, 2:1197 (May 25) 1957.
9. Rabinowitch, J.: X-rays and leukaemia. Lancet, 2:1261-1262 (Dec. 15) 1956.

Discussion

MARVIN M. D. WILLIAMS, Ph.D. (Rochester, Minn.): The general subject of this paper is not only of scientific interest at the present time but is included in national and international political issues and is being publicly debated, discussed and argued. Scientific knowledge regarding the biologic effects of radiation is scanty, particularly regarding the effects on humans, because of the difficulty in obtaining accurate and controlled data. Soon after their discovery a little more than 50 years ago, roentgen rays were found to produce some injurious biologic effects. Since that time, the philosophy relative to the problems of protection from radiation has undergone continuous evolution as knowledge regarding radiation effects and as the number of people being exposed to radiation have increased.

At first, the dangers were thought of only in relation to persons actively using x-rays and were often considered to be a necessary occupational hazard. When it was realized that others working near the x-ray machines also were being exposed, the possibility of providing some protection began to be considered. As the use of x-rays expanded and greater numbers of persons were likely to be exposed to radiations, including many who understood little or nothing about either the radiations or their dangers, it was recognized that protection must be provided and that standards of protection should be decided on. Definite efforts to determine and specify protective procedures and permissible exposures were undertaken in the 1920's. In 1928, the National Committee on Radiation Protection was organized under the sponsorship of the National Bureau of Standards, and this committee has continuously studied the problems of radiation protection and has made recommendations.

The present recommended permissible dose is less than the one specified in 1928 by a factor of between 10 and 20. The larger 1928 dose never has been shown to have produced a detectable effect in a person, but knowledge gained since then indicated that the factor of safety may have been small; therefore, it appeared advisable to reduce the recommended permissible dose. The last reduction in this dose, made about a year ago, also took into consideration the increasing number of people receiving occupational exposure, an anticipated increase in the exposure of the entire population (from such sources as shoe-fitting x-ray machines, mass thoracic x-ray survey programs, and the by-products of nuclear reactions), and the possible genetic effects that might be produced.

The problem of chief concern now is not so much the effects of radiation on the individual himself as it is the possible genetic effects that may appear perhaps 50 generations hence. The probability of genetic effects being produced depends more on the total dose received by the entire population (up to the end of the reproductive period) than it does on the dose received by any one person. The present permissible dose is believed to be less than the minimum necessary to produce detectable injury in a person, but the magnitude of the genetic effects that may be produced by even much smaller doses is still not known.

Although values for the permissible dose have been suggested by the National Committee on Radiation Protection, it must be kept in mind that there is no implication that such a dose will produce no undesirable effects, and also that it is undesirable for any person to receive such a dose unnecessarily. It is believed that no provable detectable injury will be produced in a person if his exposure is consistently less than, or even if it somewhat exceeds, the permissible dose. However, such a dose could be responsible for genetic effects in future generations and might perhaps tip the scales so that the person could be more susceptible to some disease, possibly thereby contributing to a shorter life span. More likelihood exists of damage to children than to adults from small exposures; during the first 3 months of pregnancy, the fetus is more susceptible to radiation injury than it is thereafter.

Radiation can be extremely useful as a diagnostic tool. The problem is to reach a satisfactory and reasonable compromise between the possible injuries that may become evident in the future and the probable immediate benefits to the person concerned (some additional factors enter into the application of radiation to treatment that are not relevant to this discussion). It must be remembered also that failure to use roentgenologic diagnostic procedures may cause greater harm than would be caused by the radiation.

The problems of determining what are the acceptable uses of radiation, what are permissible exposures to the entire population and what is a permissible exposure to an individual are all interrelated and also are related to many moral questions and national and international issues. Compromises are necessary, and the problem must be decided now on the basis of the present somewhat scanty knowledge. Changes will be necessary in the future, as they have been in the past, as knowledge increases and as other factors change.

The information that this study has contributed to the effects of radiation, when added to the other information already known and that to be gained in the future, will aid in the satisfactory solution of the complex problems of radiation protection. The members of this audience have an opportunity and a responsibility to continue to accumulate such data.

Medical Progress

The Pancreas and Diabetes Mellitus in Man and Animals

GERALD A. WRENSHALL, Ph.D.
Toronto, California

THE PANCREAS has long held a unique place of interest relative to clinical and laboratory studies of diabetes mellitus, since it is the only known source of the antidiabetic hormone, insulin. Its position in this regard is still a central one in spite of the recognized importance of other body factors in the initiation and course of diabetes. In this paper, attention will be limited to those studies on the pancreas and insulin being made by one of the fifteen research groups housed in the Charles H. Best Institution at the University of Toronto, the team of which I am a member. When I speak of "we" in what follows, I shall be referring collectively to members of this team.

We have been occupied in recent years with two distinct types of research on the pancreas and diabetes. On the one hand, this has included studies on the effects of insulin on the rates of transfer of metabolic factors into and out of various compartments of the living body. On the other hand, factors and conditions influencing the amount of insulin extractable by a standardized method from animal and human pancreas have been under study.

It is possible to represent a living system as an extra-cellular transfer medium in which are located groups of cells or formed elements within specific tissues between which transfer of metabolites can occur only by way of the extracellular fluid. Sheppard and Householder[15] have called such a centrally-exchanging arrangement a "mamillary" system and have developed a mathematical basis for measuring rates of transfer between compartments in such a closed system in dynamic equilibrium. We have extended their methods to measure simultaneously the rates of transfer of metabolic elements into and out of all compartments of an organism by means of isotopic tracers in the absence of dynamic equilibrium.[16] This theory has been used to measure the rates of transfer of phosphorus into and out of sixteen organ compartments in the normal rat without assuming that dynamic equilibrium exists or that rapid intermixing of phosphorus occurs in the organ compartments.[10] An example of such a mammillary system is shown in Figure 1.

The validity of this theory has been tested in a number of ways. In the first place, model hydrodynamic systems have been set up in which rates of water transfer and amounts of water in the compartments of a system were measured both directly and by means of the tracer method. The two sets of rate measurements were then compared and their magnitudes were found to agree within the limits of experimental error.[11] Secondly, it has been possible to calculate some transfer rates in mammillary systems in two ways, and these calculated rates have been found to cross-check quantitatively, both in hydrodynamic systems[14] and in the measurement of transfer rates of phosphorus in the normal rat.[10] The measured amounts of extracellular phophorus in the normal rat also have been calculated in two ways, and these calculated values have been found to cross-check closely.[10] From these measurements, the amount of intracompartmental phophorus in each of the sixteen tissues studied has been calculated. It appears likely that the intracompartmental phosphorus calculated in this way represents the intracellular phosphorus in cellular compartments, but this remains to be proven.

Measurements of transfer rates of phosphorus in alloxan-diabetic rats with and without insulin therapy have just been completed,[8] and here again the results cross-check satisfactorily. These experimental results indicate that insulin acts in the alloxan-diabetic rat to increase the rate of transfer of phosphorus from the plasma compartment into all tissues except the gonads. The increase is greatest in the cardiac and skeletal

From the Charles H. Best Institute, University of Toronto, Toronto, Canada
Extracts from a paper read before the Twin Cities Diabetes Association, November 15, 1956.

muscles and, percentagewise, is appreciably less in the liver.

The same tracer methods for analysis have been used to seek a direct answer to the question ,"How does insulin lower the blood sugar in the fasting, insulin-deprived, depancreatized dog?" It is recognized that two possible modes of action exist. Insulin may act to increase the removal of sugar from the blood into the tissues or it may act to decrease the release of sugar into the blood by means of gluconeogenesis. Both an abrupt and large increase in the rate of removal of glucose from the blood plasma and also a slow but cumulative decrease in the rate of gluconeogenesis followed the intravenous injection of insulin into the depancreatized dog deprived of insulin for sixty-six hours.[7]

These findings are of interest when compared with those of Weinhouse's group,[4] who made a similar study of the effect of insulin introduced into the blood plasma of normal dogs on the supply and removal of blood glucose. Their findings indicate clearly that the rate of influx of glucose to the blood of the normal fasting dog falls to zero when insulin is administered intravenously. A comparison of these findings indicates that a prompt stoppage of glycogenolysis is probably involved in the homeostasis of the blood sugar in their normal animals, while the suppression of gluconeogenesis by insulin is a much slower effect in the depancreatized dog.

Dr. Margaret Henderson of our team is at present measuring the rates by which glucose is supplied to and removed from the blood plasma compartment before and after the intravenous injection of another pancreatic extract, glucagon, into the fasting, depancreatized, insulinized dog. Under these conditions, glucagon causes an abrupt increase in both of these rates.

All of our tracer measurements have been made in the absence of dynamic equilibrium, and they represent measurements of the absolute rates and compartment contents involved during the adaptation to a specific stimulus in entire living systems. This kind of measurement is of fundamental interest in physiology but, as yet, is rarely seen in publication. The assumption of dynamic equilibrium made by most workers studying turnover has barred them from this type of observation.

What place do the afore-mentioned studies on the effects of insulin on diabetic rats and dogs have in a department of medical research? There is much solid ground on which the virtue of such studies in such a department can be established. However, rather than to discourse on these, I prefer to turn to the second branch of the work of

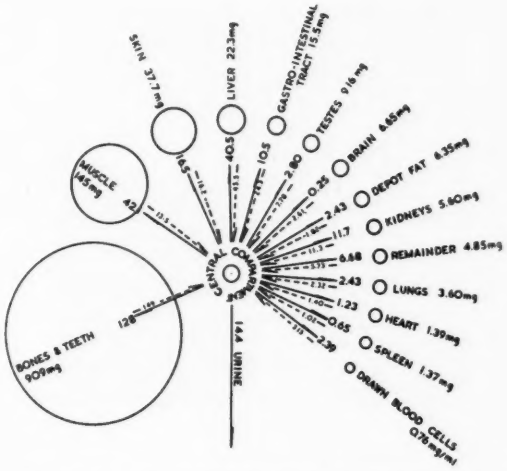


Fig. 1. Rates of transfer of phosphorus (P) in the fasting male Wistar rat with severe alloxen diabetes. All transfer rates are expressed as μg P/Min; amounts of P in each compartment are shown after compartment name.

the section. This requires no such defense since it deals largely with studies on the human pancreas. Standardized procedures for the extraction and assay of insulin from pancreases obtained at autopsy have been followed in this section for several years. The measurements obtained in this way now represent a sizable reference store of data against which the validity of many postulates concerning diabetes in man can be tested. We currently have available measurements on the insulin extractable from the pancreas at autopsy for 100 adult and seventy growing nondiabetic persons as well as for 170 diabetic patients of all ages.

These measurements clearly indicate that a gross lack of endogenous insulin is characteristic of human beings who acquire diabetes during the period of normal growth (approximately the first twenty years of life). Diabetes diagnosed thereafter differed in that a considerable amount of insulin was present in the pancreas at autopsy in a majority of such persons.[20]

It has long been recognized that the diabetes of most children differs from that in adults in that it is characterized by overheight and emacia-

tion at diagnosis, and it usually is followed by early death in diabetic coma if insulin is not given. Because of these observed differences and because of the differences between the levels of insulin in

Fig. 2. Bonny, a purebred Irish Terrier bitch which was diagnosed as diabetic at the age of two years and three months. Her daily ration is 100 gm. of cooked horse meat plus 100 gm. (dry) of K-9 meal. She receives 26 units of protamine-zinc insulin per day.

the diabetic human pancreas during and following the normal growth period in man, the term "growth-onset" diabetes was suggested to resolve the former apparently homogeneous group from the latter heterogeneous group of persons who became diabetic after the state of full stature (maturity) had been achieved.[20]

Not only did the insulin of the pancreas fall to extremely low values within a year of the diagnosis of diabetes, but the number of beta cells also fell to extremely low levels, and granulation in beta cells became practically nonexistent within the same short span of a few months in the growth-onset diabetics of our series.[24] Since positive evidence exists to support the view that the beta cells of the human pancreas are the source of endogenous insulin,[6] growth-onset diabetics appear to be diabetic due to a gross shortage of endogenous insulin.

The spontaneous diabetes of dogs shows partial parallellism to growth-onset diabetes in man.[24] Untreated spontaneous diabetes in the mature dog is associated with severe wasting, cataracts and normal sensitivity to insulin. Six of the eight dogs which had spontaneous diabetes in our studies were bitches. All but one of these were over five years old.

At the request of and with the cooperation of some of the owners, such diabetic dogs have been kept alive and well for varying periods. In every case it was possible to control the diabetes in the laboratory by use of diet and insulin. "Bonny," the youngest surviving diabetic dog on record, lives at home on a measured diet and insulin, and with periodic examinations at the Best Institute. Bonny appears to be healthy and is active (Fig. 2). The diabetes of this dog has been under such treatment and observation for nearly five years.

The insulin extractable from the pancreas at autopsy has been measured in four of the eight spontaneously diabetic dogs studied by Ricketts and associates,[13] as well as in the seven non-surviving dogs studied in Toronto. The same picture of rapid loss of extractable insulin, of beta cells and of beta cell granulation as was seen for growth-onset diabetics was found to occur in these dogs.[6,13] In these regards, the two types of diabetes appear to be closely comparable.

The alloxan-diabetes of rats also was found to be accompanied by a profound lack of endogenous insulin. Even when the diabetes of such rats had regressed until it was no longer evident, they still had a gross deficit in the amount of insulin stored in the pancreas.[22]

Nothing more than a slight indication of a decline in the average amount of insulin extractable from the pancreas with duration of diabetes for periods of up to twenty-five years has been observed in diabetic patients in whom the diagnosis is made after the normal growth period. This conclusion is based on all such persons on whom studies of insulin in the pancreas have been made; it is recognized that, while the average level of insulin in the pancreas of such persons amounts to almost half of that seen in nondiabetics similarly studied at autopsy, some of these persons have extremely low levels of extractable insulin. Thus, while some maturity-onset diabetic patients appear to have a grossly inadequate reserve of endogenous insulin, many others do not. Studies on the insulin content of blood plasma from diabetic and nondiabetic persons also indicate that lack of endogenous insulin is characteristic of diabetic children, but that frequently the plasma-insulin levels in maturity-onset diabetics are within the range of nondiabetic values.[2]

Is there a form of spontaneous diabetes in animals similar to that in mature man in which gross deficiency of insulin is not seen? Studies have

been proceeding with the cooperation of Dr. Jean Mayer and his associates, of Harvard University, on the insulin extractable from the pancreas of the obese-hyperglycemic mouse, with this possibility in mind. In this type of animal, high levels of pancreatic insulin relative to those seen in nonobese control sibs were repeatedly observed. There was no evidence that this form of "diabetes" caused or resulted from a subnormal supply of insulin or that the "diabetes" caused or resulted from reduction in the number of islet cells with long duration of the condition. On the contrary, hyperplasia of islet cells was present.[17] Shortly after such animals received injections of growth hormone, the level of blood sugar was further elevated. At that time, a fall was observed in the insulin extracted from the pancreas of the obese-hyperglycemic mouse, the fall being proportional to the magnitude of the increased elevation of the blood sugar caused by growth hormone.[3]

Several factors in the human pancreas in addition to the extractable insulin have been studied and are under study. The extent of beta cell granulation that could be demonstrated by special histologic stains has been compared with the concentration of insulin extractable from other sections of the same pancreas, and a significant 1:1 correlation between these two factors has been observed for both nondiabetic and diabetic persons.[6] This confirms the similar findings of Bell[1] and represents added evidence that, in human beings, these stainable granules in the beta cells are manifestations of insulin.

During the past two years, considerable interest has attached to the lowering effect on blood sugar in man of orally administered carbutamide and tolbutamide. Extensive studies of this type of response have been made in Europe and on this continent. The findings of Mirsky and coworkers[12] are of special interest in this regard, particularly since they were reached objectively through the application of recognized statistical procedures. These authors measured the decrease of blood sugar during the first six hours after administration of a single oral dose of tolbutamide to 200 living diabetic patients of both sexes and all ages. They concluded that (1) practically all growth-onset diabetic patients except those who are newly diagnosed, are much less responsive to the hypoglycemic action of this drug than are those diagnosed after the age of forty, (2) responses in persons diagnosed as diabetic within the age range of twenty to forty years are intermediate in degree, (3) little relationship exists between effectiveness of response and duration of diabetes in the older patients, and (4) no detectable sex difference occurs in the response to the tolbutamide test.

Striking similarities are noted between these findings and the levels of insulin extractable at autopsy from the diabetic human pancreas. Corresponding to points (1) and (4) of Mirsky's group, it has been reported that the level of insulin extractable from the pancreas in growth-onset diabetic patients falls within months to characteristically extremely low levels in all but newly diagnosed patients,[24] but it is much higher and is insensitive to the duration of diabetes in maturity-onset patients.[20] We recently reported a sex difference with a moderate degree of statistical significance in the insulin extractable from the pancreas in persons diagnosed as diabetic in the twenty to forty-year range.[18,23] The female patients in our series who were diagnosed as diabetic in this age-range had appreciable pancreatic stores of insulin, while the corresponding males had very little. Evidence has been presented[23] indicating that the apparent disagreement with the conclusions of Mirsky's group on this point developed as a result of appreciable differences in the average duration of diabetes in the two series.

Comparisons of the levels of insulin extractable from the diabetic human pancreas with the proportion of diabetic patients responding to oral use of carbutamide have been made on the basis of age at diagnosis and known duration of the diabetes.[18] This comparison, together with the one already described, favors the hypothesis that a significant supply of endogenous insulin is required for carbutamide or tolbutamide to normalize the amount of blood sugar in diabetic man.

We have gathered information concerning the effect of the interval between death and autopsy on the amount of insulin extractable from the human pancreas. Instead of values that declined steadily with the time of aging, an early rise and a subsequent fall were noted in the insulin extractable from samples of human pancreas during aging at 4° C.[6] The same phenomenon has been observed in fresh beef pancreas under more closely controlled conditions[9,19,21] The experiments thus far indicate that the initial rise may result from

the synthesis of insulin and its accumulation in the initially fresh pancreas in the absence of circulating blood. The phenomenon appears to be closely related to the similar findings of Grodsky and Tarver[5] observed during the incubation of fetal beef pancreas.

In conclusion, I would like to speak briefly about the team to which I am attached. It is composed mainly of young people, containing approximately equal numbers of men and women. Its members are drawn together from widely distributed parts of the world by common interests in problems of carbohydrate metabolism.

Ideas are precious commodities with which research teams work; unless care is taken to prevent it, the origin of such ideas may become a matter of question after weeks or months. Particular care is taken to avoid such difficulties by maintaining a series of "Idea Books" in which new ideas are duly entered, signed and dated at the time of their origin, regardless of whether such ideas do or do not appear to be important. In this way, a pool of research ideas is open to all members of the team, and ideas beget ideas. There is also an essential spirit of friendly competition among members of the team to register new ideas, and this is good for all concerned.

Not all projects launched by the team have been successful, and I think it is necessary to be frank about it. For example, one student and I worked together for over a year on measurement of the transfer rates of phosphorus in the mouse. The results of this experiment did not cross-check since the tracer phosphorus had been injected in a non-physiologic form, and the findings had to be shelved.

A very important member of each of the teams currently engaged in medical research at the Institute is Dr. Best. The selection of the various people who make up these teams is in his hands, and the degree to which he is able to keep in touch with the detail of projects that are continuing in the Institute named after him is remarkable. We are indebted to him not only for many valuable suggestions but also for direct participation in some of the experiments and for the "tying together" of our projects and findings with those of other teams and other research centers. He is indeed a leading and contributing member of our team. As one who is diabetic, it is a special privilege for me to be a member of his group in the hunt for a killer that is still at large.

References

1. Bell, E. T.: The incidence and significance of degranulation of the beta cells in the islets of Langerhans in diabetes mellitus. Diabetes, 2:125-129, 1953.
2. Bornstein, J., and Lawrence, R. D.: Two types of diabetes mellitus with and without available plasma insulin. Brit. M. J., 1:732, 1951.
3. Clarke, D. W., Wrenshall, G. A., and Mayer, J.: Effects of pituitary growth hormone on the insulin and hyperglycemicglycogenolytic factor extractable from the pancreas of obese-hyperglycemic mice. Nature, 177:1235, 1956.
4. Dunn, Doris F., Friedman, Bernice, Maas, A. R., Reichard, G. A., and Weinhouse, S.: Effects of insulin on blood glucose entry and removal rates in normal dogs. J. Biol. Chem., 225:225-237, 1957.
5. Grodsky, G., and Tarver, H.: Paper chromatography of insulin. Nature, 177:223-225, 1956.
6. Hartroft, W. S., and Wrenshall, G. A.: Correlation of beta-cell granulation with extractable insulin of the pancreas. Diabetes, 4:1-7, 1955.
7. Henderson, Margaret J., Wrenshall, G. A., and Odense, P.: Effects of insulin on rates of glucose transfer in the depancreatized dog. Canad. J. Biochem. & Physiol., 33:926-939, 1955.
8. Koike, G., Lax, L. C., Salter, J., and Wrenshall, G. A.: Simultaneous rates of phosphorus transfer between sixteen organ compartments in the alloxan diabetic rat with and without insulin. National Biophysics Conference, Columbus, Ohio, Mar. 3-4, 1957. Abstracts, p. 38.
9. Labuschagne, C. J., Haessig, B. K., and Wrenshall, G. A.: Factors influencing the amount of insulin extractable from beef pancreas II. Effect of altering the extraction procedure on the changes in the insulin extractable from aging pancreas and on recovery of insulin. Canad. J. Biochem. & Physiol., 35:537-544, 1957.
10. Lax, L. C., Sidlofsky, S., and Wrenshall, G. A.: Compartmental contents and simultaneous transfer rates of phosphorus in the rat. J. Physiol., 132: 1-19, 1956.
11. Lax, L. C., and Wrenshall, G. A.: Measurement of turnover rates in systems of hydrodynamic pools out of dynamic equilibrium. Nucleonics, 11:18-20, 1953.
12. Mirsky, I. A., Diengott, D., and Dolger, H.: The relation of various variables to the hypoglycemic action of 1-butyl-3-p-tolylsulfonylurea in patients with diabetes mellitus. Metabolism, 5:875-893, 1956.
13. Ricketts, H. T., Peterson, E. S., Steiner, P. E., and Tupikova, N.: Spontaneous diabetes in the dog: an account of eight cases. Diabetes, 2:288-294, 1953.
14. Schachter, H.: Direct verus tracer measurement of transfer rates in a hydrodynamic system containing a compartment whose contents do not intermix rapidly. Canad. J. Biochem. & Physiol., 33:940-947, 1955.
15. Sheppard, C. W., and Householder, A. S.: The mathematical basis of the interpretation of tracer experiments in closed steadystate systems. J. Appl. Physics, 19:510-520, 1951.
16. Wrenshall, G. A.: Working basis for the tracer measurement of transfer rates of a metabolic factor in biological systems containing compartments whose contents do not intermix rapidly. Canad. J. Biochem. & Physiol., 33:909-925, 1955.
17. Wrenshall, G. A., Andrus, S. B., and Mayer, J.: High levels of pancreatic insulin coexistent with hyperplasia and degranulation of the beta cells in mice with the hereditary obese-hyperglycemic syndrome. Endocrinology, 56:335-340, 1955.
18. Wrenshall, G. A., and Best, C. H.: Extractable insulin of the pancreas and effectiveness of oral

(Continued on Page 362)

Case Presentations

Rupture of Vaginal Varicosities Simulating Placenta Previa

WM. E. TAYLOR, M.D.
Minneapolis, Minnesota

THE LITERATURE carries little on the subject of ruptured vaginal varicosities which resemble placenta previa. The importance of making this differential diagnosis prompted the following presentation.

Case Report

Mrs. K. A., age thirty-two, was seen for the first antenatal visit of her third pregnancy on May 14, 1956. Her last menstrual period had occurred on February 1, 1956 and was normal. The patient complained of amenorrhea, mild nausea, and abdominal "fullness."

General physical examination revealed a well-developed, slight, white woman weighing 114 pounds. Blood pressure was 112/60. A small lymph node was palpable in the right axilla. The breasts were full and slightly tender. The cervix was livid and soft. The uterus was anterior and fourteen weeks' gestational size. There were moderate varicosities of the left leg along the superficial saphenous distribution. Hemoglobin was 13.2 grams/100 ml. Pelvic mensuration and evaluation was done and found adequate for vaginal delivery. Remainder of the examinations were essentially negative. A diagnosis of normal intrauterine pregnancy was made, and the patient was given an E.D.C. on November 8, 1956.

On subsequent prenatal visits no complaints were made except for occasional reference to varicosities in the left leg. These were asymptomatic while using an elastic stocking. There were no complaints or abnormal findings referable to the vulva or vagina.

About 6:00 p.m. on August 29, 1956 (thirty weeks' gestation) the patient sat down on a chair and a pool of blood formed in the chair. She became faint and weak and was put to bed immediately by her husband. An ambulance was dispatched, and the patient arrived at the hospital at 7:15 in the evening. She was admitted to the delivery room and examination revealed moderately heavy vaginal bleeding with large clots formed at the vestibule extending into the vagina. Pelvic examination was deferred until blood was available.

The fetal heart tones were regular and of good quality. There were no uterine contractions and no tenderness was present. The blood pressure was 120/70. One thousand cc. of 5 per cent dextrose in distilled water was started intravenously with a Y-tube transfusion apparatus. Immediate cross match and hemoglobin determinations were ordered. A perineal prep was ordered, during which the bleeding became more severe. The patient was then transferred to surgery where preparation for a Cesarian section had been arranged on the presumption that the diagnosis was most likely a placenta previa, because of the severe painless bleeding in the latter part of pregnancy. At this time (8:30 p.m.) the hemoglobin was reported as 10.4 grams/100 ml., and one pint of blood was attached to the intravenous setup. Bleeding time was reported 1′ 56″ and coagulation time was 15′ 15″. Although the patient appeared pale, the blood pressure maintained itself at 120/60. The vaginal bleeding again was noted to have slowed to a moderate flow.

After some discussion as to whether the routine presurgical vaginal examination should be foregone, it was decided that the fetal and maternal condition would not be jeopardized by this procedure, so this was done. After removal of the clots at the introitus, a vaginal speculum was introduced. It was noted that the upper two-thirds of the vagina was completely free of blood. Further inspection revealed free bleeding from the right postero-lateral vaginal wall just within the hymenal ring. A plexus of varicosities was noted to protrude in this area. The bleeding points were clamped with Kelly hemostats and the varicosities were closed at several points with interrupted sutures tied over the vaginal mucosa. The bleeding was entirely stopped by this procedure, and it was felt that the pregnancy could safely be allowed to progress to a normal vaginal delivery if no further complications were encountered. The total blood loss was estimated to be in excess of 2,000 cubic centimeters.

A second pint of blood was given after surgery was completed. A placentagram was taken on August 30, 1957 and was negative for placenta previa. The hemoglobin on the third postoperative day was 12.0 grams 100 ml. The patient made an uneventful recovery and was discharged on the fourth postoperative day (September 2, 1956).

The patient had no further complications. Frequent inspection of the operative site revealed excellent healing with no residual varicosities. Delivery occurred at term (November 6, 1957), without incident. The baby weighed 8 pounds 6 ounces. A midline episiotomy was used. The patient again recovered uneventfully and was discharged on the fourth post-partum day.

(Continued on Page 362)

Recurrent Lower Leg Ulcers in Lupus Erythematosus

ROBERT W. GOLTZ, M.D.
NADINE G. SMITH, M.D.
Minneapolis, Minnesota

IN ORDER to call attention to recurrent infarctive lower leg ulcers as part of the syndrome of lupus erythematosus, the following case report and brief review of the literature are presented.

Case Report

Mrs. G. W., a white housewife, aged forty-five, developed an erythematous eruption on the butterfly area of the nose and cheeks at age nineteen. This eruption was accompanied by swelling and pain in the joints of the hands. A diagnosis of lupus erythematosus, confirmed by cutaneous biopsy, was made by Dr. H. E. Michelson, and treatment with injections of gold salts was instituted. This was followed by temporary disappearance of the eruption and joint symptoms, but there were periodic exacerbations of the skin lesions for the next seven years. At age thirty-five she developed symptoms of numbness in the fingers and toes after exposure to cold. The Raynaud-like symptoms have persisted to date, but have never been very severe. There has been no actual pain or trophic changes in the digits.

At age twenty-eight, Mrs. W. developed the first of a series of leg ulcers. New ulcers have appeared periodically since, at the rate of one or two new lesions each year, so that she has now had a total of over twenty, all near the ankle joints. The ulcers appear rapidly, starting as an area of bluish-red discoloration of previously normal skin. At this stage (and later) there is severe pain in the involved area. There is no swelling, but within a few days the discolored areas become necrotic and an ulcer forms. These ulcers average 2 to 3 cm. in diameter, extend as deeply as the periosteum, and are extremely indolent, usually taking several months to heal.

Prior to the use of corticosteroids in the treatment of these ulcers, a number of different remedies were unsuccessfully tried. These included prolonged bed rest, numerous local applications, enzymatic debridement, a number of different antibiotics, such vasodilating drugs as tolazoline hydrochloride (Priscoline) and dibenzylene, and attempts at skin grafting. In 1945, a right lumbar sympathectomy was performed, following which the ulcers then present on the right ankle promptly healed. Subsequently, however, there have been as many ulcers on the right leg as before, and the patient states that they have been more painful than those on the left leg.

Physical examination shows a slender white woman who appears well except for her leg lesions. There is a slight malar flush, apparently the result of diffuse superficial telangiectasia of that area, but no frank lesions of lupus erythematous. The blood pressure is normal, and the liver and spleen are not palpable. The fingers are somewhat cold, but show no blanching or cyanosis, and no trophic changes. The right leg is somewhat warmer than the left, but good pulsations are palpable in both.

At the present time, an ulcer is present on both ankles, and numerous scars mark the sites of former lesions (Figs. 1 and 2). The ulcers measure aproximately 2 x 3 cm., are sharply punched out, deep, indolent, and filled with necrotic debris.

Laboratory studies have been carried out on several occasions. Hemoglobin, red blood cell count, hematocrit and color index have always been within normal limits. The leukocyte count has varied from 5400 and 6850 cells per cubic mm., with a normal differential count. The urine has been normal except for a reported trace of albumin on one occasion. Serologic tests for syphilis are negative.

Tests for cryoglobulin have given negative results on two occasions. Electrophoretic fractionation of serum proteins gave the following results: total protein 7.6 grams per cent, albumin 3.3 grams per cent, globulin 4.3 grams per cent and gamma globulin 2.1 grams per cent.

Tests for lupus erythematosus (L.E.) cells in the peripheral blood have been done on three occasions, in three different laboratories. The first two tests were negative, but the most recent, carried out by Dr. Dorothy Sundberg, showed L.E. cells.

For the past six weeks this patient has been treated with prednisone, 20 mgm. daily. In spite of the fact that she has not been confined to bed, the ulcers have gradually filled with granulation tissue and have almost completely epithelialized from the edges.

Comment

Recurrent ulcers of the lower legs have not been commonly regarded as part of the syndrome of lupus erythematosus, and have not been mentioned in any review of that disease known to us. However, several indirect references to such an association appear in recent literature.

In 1952, Barker[1] presented before the New York Academy of Medicine the case of a woman with

From the Division of Dermatology, University of Minnesota Medical School, Minneapolis, Minnesota.

recurrent pretibial ulcerations in whose blood L.E. cells were found. In the same year, Schoch,[2] in describing leg ulcerations in Felty's syndrome, reported a patient whose bone marrow contained L.E. cells. Schoch mentioned the possibility that some cases of Felty's syndrome may, in fact, be instances of latent lupus erythematosus. Gaté, et al,[3] presented a patient with chronic arthritis and recurrent leg ulcers, the vascular changes of which were thought to resemble those of periarteritis nodosa. There was marked leukopenia, however, a finding more suggestive of lupus erythematosus than of periarteritis nodosa.

Early in 1957, Allison and Bettley,[4] under the title "Rheumatoid Arthritis with Chronic Leg Ulceration," reported six patients with arthritic symptoms and recurrent leg ulcers, some of which were strikingly similar to the ulcers in our patient. Four of these six patients were found to have positive tests for L.E. cells, and these authors commented on the strong possibility that the "rheumatoid" arthritis in these patients may have been part of the lupus erythematosus syndrome.

The reason for the appearance of these ulcers, and for their slowness in healing, remains unknown. Those we have observed in our patient, and others reported in the literature, resemble, in their early stages, localized infarctions of the skin and subcutaneous tissues. This suggests occlusion of some large arteriole, either by thrombosis or spasm; however, the failure of these ulcers to heal over long periods of time, and their rapid response to corticosteroids, suggest that some mechanism other than simple vascular occlusion is involved.

Unfortunaely, histologic study has given little information. Various vascular and connective tissue changes have been reported, but are probably secondary alterations. It would seem that any histologic examination short of serial sectioning of an entire lesion (and only in its early stages) would be quite meaningless. Unfortunately, such a complete study has not been practicable up to this time.

Summary and Conclusions

A patient with recurrent, slowly healing ulcerations of the lower legs, associated with long standing lupus erythematosus, is reported. Several similar cases have been found in the literature.

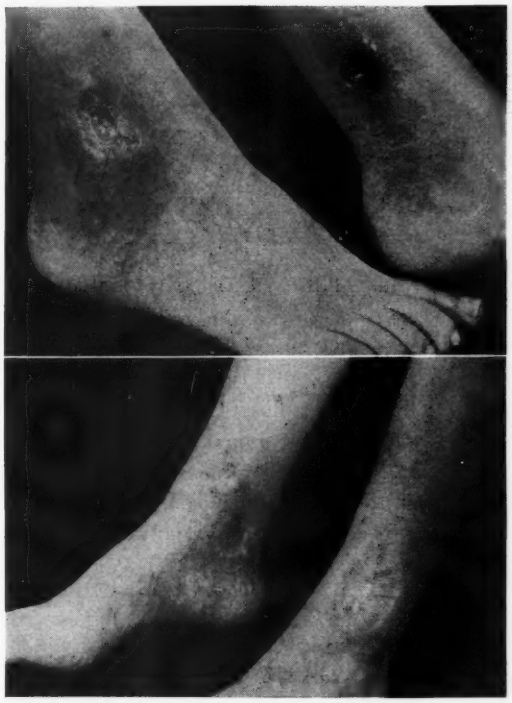


Fig. 1. (*above*) Old ulcer on lateral right ankle, and more recent ulcer on medial left ankle.

Fig. 2. (*below*) Numerous scars, marking sites of former leg ulcers.

After failure to respond to other therapeutic measures, rapid healing followed administration of corticosteroids.

It is believed that these lesions should be considered part of the syndrome of lupus erythematosus.

References

1. Barker, Leslie P.: Disseminated lupus erythematosus with leg ulcers (Case presentation at the meeting of the New York Academy of Medicine, Section of Dermatology and Syphilis, March 4, 1952). A.M.A. Arch. Dermat. & Syph., 66:758 (Dec.) 1952.
2. Schoch, Eugene P., Jr.: Ulcers of the leg in Felty's syndrome. A.M.A. Arch. Dermat. & Syph., 66:384 (Sept.) 1952.
3. Gaté, J., Vayre, J., and Saint-Cyr, M.: Ulcères de jambe atypiques avec formule histologique rappelant la périartérite noueuse (Case presentation at the meeting of the French Society of Dermatology and Syphilology, June 26, 1953), Lyon Med., 189: 158 (Sept.) 1953.
4. Allison, J. H., and Bettley, F. Ray: Rheumatoid arthritis with chronic leg ulceration. Lancet, 272: 288 (Feb. 9) 1957.

Tumor Conference

Section Editor
CLAUDE HITCHCOCK, M.D.

CASE STUDY, MINNEAPOLIS GENERAL HOSPITAL

Pain in her back and hips caused the patient, aged sixty-five, to consult her physician four months prior to the time of her admission to the Minneapolis General Hospital. After several months' effort to establish a definitive etiology of the back pain, a mass was discovered in the right breast.

Examination at General Hospital revealed a bed-fast woman with no history of having previously been aware of the mass in the breast. During several months, the patient had lost between 35 and 40 pounds, and the pain in her back and hips had become progressively worse. Physical examination revealed a mass measuring 3 by 4.5 cm. in the outer upper quadrant of the right breast which was fixed to the underlying musculature. A large fixed nodule was present in the right axilla, but there were no palpable supraclavicular nodes.

The liver was slightly enlarged, but smooth and non-tender. Blood studies revealed a normal hemoglobin and differential count. The patient had a few pus cells in the urine and a blood urea nitrogen of 11. The liver profile chemical studies were within normal limits. The alkaline phosphatase, however, was 26 King Armstrong units, representing a marked increase, and the acid phosphatase determination was 2.9 King Armstrong units. A serum calcium of 12 mg. per cent was found, with a phosphorus of 3.7 per cent.

Roentgen studies of the skeleton revealed multiple rib fractures and diffuse involvement of the skeletal system with osteoblastic and osteolytic metastases.

Upon admission to the hospital, the patient was taking premarin in a low dosage. This had been started several days prior to admission. Since this patient came to the hospital with probable breast carcinoma with widespread distant metastases, a program of hormone therapy was considered. The patient first had a single incisional biopsy of the mass in the right breast which proved to be a primary adenocarcinoma.

She was started on stilbestrol therapy, 5 mg. three times daily, and after several weeks a balance study of her calcium metabolism was undertaken. While on a daily total calcium intake of 200 mg. or less, the patient excreted from 109 to 277 mg. of calcium per day. After six weeks of stilbestrol therapy, the hormone was discontinued and one month later the calcium excretion studies revealed the daily urinary calcium to vary from 28 to 82 mg. (while the patient was on a daily diet of 200 mg. of calcium or less). It was the consensus of the staff that this patient responded in a negative manner to the estrogen therapy and this form of hormone treatment was contra-indicated. The patient then received x-ray therapy to the involved areas of weight bearing bones, and improved somewhat with relief of pain for a period of several months.

The patient re-entered the General Hospital during December, 1956, with increased pain and discomfort. A daily regimen of a 200 mg. calcium diet was started on December 28 and was continued for nine days. During this period, the urinary calcium excretions varied in the neighborhood of 76 mg. of calcium per day. Testosterone propionate in a dosage of 75 mg. was started on January 4, 1957, and was given twice a week until January 22. The patient received a total of six doses of testosterone propionate. The calcium balance studies were again started on January 17, 1957, and four determinations ranged from 87 mg. per day to 346 mg. per day. It appeared that this patient was again having an exacerbation of the bony metastases by the administration of testosterone propionate and therefore this hormone therapy was stopped on January 22.

It is well known that approximately 35 per cent of patients in the postmenopausal age group, who are placed on estrogen therapy for metastatic breast disease, will respond objectively to hormone therapy. It is also well established that about 25 to 30 per cent of patients with bony metastases will respond in an objective manner to estrogen therapy or to testosterone therapy. It is entirely conceivable that, on occasion, we can do harm to patients by administering hormone therapy when it actually has an adverse effect by fostering tumor growth. The use of calcium balance studies to determine the efficacy of hormone therapy can be recommended, although it is a costly and time-consuming procedure. Under the programs of charity type hospitals, however, where patients are hospitalized for prolonged periods of time, this program is feasible. The results in this patient would indicate that both estrogen therapy and testosterone propionate therapy were contra-indicated because of the unfavorable biologic characteristics of the metastatic breast cancer in this instance. The patient continued to worsen and subsequently died of the disease.

Editorials

JOHN F. BRIGGS, M.D.
ARTHUR H. WELLS, M.D.
HENRY G. MOEHRING, M.D.

WMA AND WHO

The Difference

1. WMA is an organization of national medical associations. The unit of membership is the most representative national medical association in each country. It is completely non-governmental. It is not part of the U. N. It is a voluntary organization.

2. WMA represents the practicing medical profession.

3. WMA was organized in 1947 by AMA representatives and Western European medical leaders. Purpose was to exchange medical knowledge, to protect the freedom of medicine, and promote world peace.

4. Each member association sends two delegates, two alternate delegates and observers to the General Assemblies—the supreme policy making body of WMA.

5. The executive body of WMA is the Council. This meets twice a year and comprises 11 members elected from the Assembly and the President, President-Elect and Treasurer.

6. WMA is supported by members' dues and contributions and the annual budget is about $165,000.

7. American physicians and allied corporations interested in the work of WMA are organized as the United States Committee of The World Medical Association.

1. WHO is an intergovernmental health agency. The members are the governments that accept the nine principles upon which WHO is founded.

2. WHO represents governments in their public health and medical activities.

3. WHO is the result of proposal of U. N. in 1945 to create a specialized agency to deal with all matters related to health on a world-wide scale.

4. Each member government sends three delegates, chosen preferably from the national health administration of the government, to the annual World Health Assembly.

5. The Executive Board of WHO is the executive body and consists of 18 members elected to represent 18 member governments.

6. WHO is supported by dues allocated by the U. N. scale and the budget for 1958 is $13,000,000.

7. American citizens interested in the work of WHO are organized as the Citizens' Committee for the World Health Organization.

CLINICAL PSYCHOLOGY—HISTORY

The opportunity to state the case of clinical psychology is a welcome one. This editorial will deal with historical background. The next will explore the current status of the field, particularly in Minnesota. The last will involve guesses as to the future pattern of the profession.

The heritage of clinical psychology goes back over eighty years to the University of Leipzig and to Harvard in this country. Its parents were philosophy and physiology; and for an understanding of psychology today it is well to keep in mind that its birth, and most of its maturing process as well, took place within the academic setting. Scientific thought, inquiry, and experimentation were in the strict academic tradition; and contact with the medical school and sick people has been a development largely of the past two decades. Most of the earlier work (and much of the present) involved animal experimentation at a basic level. How the experimental animal work, researches in conditioning and learning, for example, might apply to suffering humanity, if it applied at all, was not a conspicuous preoccupation of psychology during its first half century. Thus the psychologist, until quite recently, was a university scholar with his office in or next to his laboratory which often contained an animal colony with much physical equipment. If he knew members of the clinical medical faculty of his university, it was usually through mutual interest in physiology, anatomy, or general biology. He would usually be well known in the university machine shop, for he often made much of his own equipment. These years laid a firm foundation for controlled experimentation and scientific tradition.

In view of such a background, how did the specialty of clinical psychology develop? This can be traced largely to that parent aspect of psychological research which related to the testing of intelligence. The early work of Binet and Simon led to standardized tests of intelligence, the scores of which were then related to chronological age to provide the intelligence quotient (I.Q.). As these tests came into use, it followed that they would be valuable in the diagnosis of mental deficiency and herein the psychologist began to associate with the physician. This first relationship occurred in the pediatric age group and hence the first "clinical" psychologist was found in institutions and clinics diagnosing or caring for children. In World War I derivatives of these tests were spectacularly applied for the screening of adult men. The various measures of intelligence are now so well established that it would be a poor children's clinic indeed that did not have such tests available to it. In any event, this development saw the birth of the "clinical" psychologist, i.e., the psychologist being used in the medical setting.

It was not a big step from intelligence tests to tests for personality, and this aspect of testing came into prominence, together with testing for aptitudes, during World War II. We can be proud of the fact that some of the significant research in personality testing was done at the University of Minnesota. Williamson, Paterson, Hathaway, and McKinley are names internationally famous in this field. The Air Force particularly was much interested and extensively used personality and aptitude tests in the selection of flying personnel. The Army and Navy did likewise for their people.

Thus the psychologist of today who does research, teaching, and service in the hospital and clinic traces his ancestry directly to the academic tradition; his intellectual heritage is a fusion of philosophy and physiology. His entrance into the clinical setting began with intelligence tests, standardized on "normals" but which found ready application in measuring the extremes of intelligence, i.e., the bright and the dull. In this context, the psychologist found himself working with physicians caring for children and aiding them in diagnosis. The "clinical" psychologist was born.

DONALD W. HASTINGS, M.D.

ABOUT PRINTERS

I suffered so much from printers' errors
That death for me can hold no terrors.
No doubt this stone has been mis-dated.
I wish to Christ I had been cremated.
(Daniel George's *New Epitaphs*, c. 1957)

This epitaph mildly expresses what any writer feels when he finds printers' errors in his deathless prose or poetry. Impatience with mistakes in printing quickly grows into bitter intolerance of the printer when the writer realizes how many thousand times the error was repeated and how permanently it stands there for everyone to see. Further fuel is added to the hot hate by the aforesaid everyone's happy eagerness to carry the error to the author and to remark cuttingly about it.

We plead for temperance toward the printer and cite these data in support of such moderation: Each of the letters, spaces, punctuation marks, et cetera in your masterly production reaches the printed page via a little piece of metal, maybe several pieces of metal—the type bar on the typewriter, the matrix in the typesetting machine, and the bits and squiggles inserted to maintain spaces, call attention to footnotes, and other pertinent information. This page, for example, involves at least 5000 such pieces of metal, some of them so small that they are handled with tweezers because fingers are too thick or clumsy. Not only must each of these bits of metal be in the right place at the right time in the process of getting this into print, but every time the type for the page is moved, the risk of disarranging some of them arises. And if the first setting of the type proves to have an error in it, the resetting to correct the error may also disarrange the metal pieces to yield a greater error than the one corrected.

No matter how much of their work printers try to reduce to foolproof typesetting, somewhere along the line you always come back to individual pieces of metal and thus printers remain craftsmen who, on each page of type, have over 5000 possibilities of making a mistake. Like us, fully aware that attaining perfection consistently is impossible, they nevertheless continue to strive to attain it. That they succeed so often in producing an errorless page is the wonder which you can afford to feed your outraged ego when you find a mistake in *your* article.

H.G.M.

MEDICAL LIBRARY SERVICES

Doctors who use medical libraries in this second half of the twentieth century have an assurance of what they want in the way of materials and of services from them. Through the growing adequacies of collections and services in medical school libraries, many physicians are graduated from their alma maters with definite concepts of what materials should be in the library, how they may be found, which includes short cuts, card catalogs, indexes and abstracts, and where they may be found.

All that a physician expects of a medical library, whether it is operated under federal, society, industry or hospital auspices, the librarian has the responsibility and the privilege of providing for him. He may then expect orientation to the particular library which he has selected to use. Again considering variations in individual libraries the new patron may be shown a floor plan of the library on which is indicated the library's important tools of communication, card catalog, indexes, abstracts and the location of reference, journal, reading room and stack divisions. A tour will lead him specifically to the locations of these important sources of information. Some explanations in detail may be in order. The dictionary catalog, which is the index to the library's complete holdings of books and periodicals, and especially if it varies in arrangement from the standard subject-author type, will be fully explained. If the student or practitioner has a limited knowledge of bibliographic tools, the underlying principles should be reviewed with him. Care must be taken that the use of such important indexes as the Current List of Medical Literature, whose entry forms deviate from other indexes, is understood. Any extra indexing project that the library carries should be pointed up as the important access to the current information actually in the library.

A potential client should be given a copy of the library's policies which informs him of the hours for service, the length of loans, the policy for borrowing books as supplementary material from other libraries. Also he will need to know if the library offers an extensive bibliographic service including translation and the editing of papers and where these may be obtained if the library does not provide them.

In a large library which will necessarily be supported with adequate funds, or nearly so, physicians may hope to find practically all their current reference wants. If the institution has a research program, the library will be geared to support it. Doctors are entitled to find in small libraries an adequate up to date working collection of standard textbooks and monographs in fields in which the institution does its major work. The larger the affiliating institution and the farther away the library is from larger collections in medicine, the more extensive its development must be in all subject fields. A medical library usually allocates two-thirds of its fund for the purchasing of current journals. This periodic material, because of the speed of scientific investigation, is every doctor's reading prerogative.

Another important, although possibly not essential, aspect of library service is pleasant surroundings. More and more libraries are moving into areas and furnishings conducive to relaxation and concentration. However, if a choice were to be made between a well-organized, carefully selected collection housed in gloomy, unattractive surroundings and a modern or elaborately furnished room with a meager collection of out-dated books, the preference would be surely for the former. Fortunately, libraries are keeping pace with modern trends in architecture and furnishings. Acoustic tiles and comfort cooling are making almost any location acceptable for the library, providing it is reasonably convenient to the main streams of traffic within the institution. Adequate lighting, comfortable chairs and reading lamps, private study units, or carrells, and open stacks for browsing rank high as aids to study, for practitioner, student and research worker alike.

Within this world of "miles of print" the difference is not so much whether the collection is large or small, clinically practical or directed toward research, as how it is organized and administered. This reverts again to the human components in library service, the librarian and her staff. If a poll were taken to evaluate the effective services of any medical library, the librarian's friendly, willing and co-operative attitude might rank high on the scale of appraisal as indicative of what doctors want, expect and really need from their libraries.

SISTER TERESA LOUISE
Medical Librarian

LIFE INSURANCE IN ESTATE PLANNING TODAY—III

Should Life Insurance Policies Play a Bigger Role in Your Estate?

Under the new tax law, it is possible to avoid estate tax on the proceeds of policies taken out on your life even though you pay all the premiums. The basic requirements are: (1) the proceeds must be payable to a beneficiary other than your executor or your estate; (2) you must have no strings on the policy that the law will view as incidents of ownership.

These requirements would be met, for example, by naming your wife or child as beneficiary, and transferring the policy with all incidents of ownership to either the beneficiary or a trustee.

The only estate tax danger in this arrangement lies in the possibility that the Treasury will claim that you transferred the policy or paid the premiums "in contemplation of death." But this danger is completely removed if you live more than three years after the policy transfer and the last premium payment. And even if you were not to live three years after the last premium payment, the probability is that most of the proceeds would escape estate tax.

When *new* insurance is purchased and the wife is the applicant, the owner and the beneficiary, the "contemplation of death" provision no longer applies.

Note that you can avoid gift tax on transfers of policies through use of the $30,000 over-all exemption and the $3,000 annual exclusion. And if you are married, you can transfer free of gift tax to one beneficiary a partly or fully paid-up policy worth up to $66,000. Payment of premiums on a transferred policy would also be tax-free up to $6,000 annually (plus any additional premiums for which the over-all exemption is used). The policy does not have to have a cash surrender value to qualify for the annual exclusion.

Should Income Shifting Play a Part in Your Estate?

A means of achieving a "triple tax" saving (Income, Estate and Inheritance) is the use of the Short Term Trust, using the trust income to purchase life insurance on the life of the mother or on the children themselves. The father sets aside some securities or property, and has the income therefrom payable to a trust, administered by a disinterested trustee. The trustee uses the trust income to purchase life insurance policies on the lives of the children. The trust may be for the life of the beneficiary or for any period ten years or over.

So we find a four-way tax saving:

1. The trust pays the tax on the income received in the trust shifting the tax out of the father's high bracket to the lower bracket of the trust.
2. If the grantor's wife is named beneficiary of the life policies on the child, and the child dies during the trust period, $4,000 of the proceeds pass free of state inheritance taxes.
3. If the trust income is less than $675 to each child, or the child is under 19 or a student and receives over half of his support from his father, then the grantor will not lose the tax exemptions. The trust also receives a $100 tax exemption in and of itself.
4. If the grantor dies while the trust is in operation, a certain portion of his estate has been cut away with a subsequent lower estate tax.

Three items you should be careful about; the trust must be set up for ten years or more, or for the life of the beneficiary and the grantor must not be the insured, and the trust income should not be used for support of the child which would make the trust income taxable to the grantor.

ALAN W. GILES

THE USES OF WAXED PAPER FROM A MEDICAL STANDPOINT

Most of us think of waxed paper in terms of the familiar household roll that is so handy for everyday kitchen and household chores. But the greatest use of waxed paper in today's living is as a flexible packaging material that offers many outstanding advantages to its users.

Waxed paper is a leading package wrap for most processed foods and food products, those items which are of vital concern to the health and well-being of everyone. It provides full flavor and freshness protection, along with established sanitation "plusses."

Bread and other baked goods products are most often packaged in waxed paper. Indeed, 82 per cent of all white enriched bread is waxed paper-

wrapped, as are many of the specialty health, vitamin and protein breads that are of growing popularity in people's diets. In addition, most crackers, biscuits and cereals are wrapped in waxed paper, or packaged with waxed paper or waxed glassine inner wraps. Even butter and other dairy products are being packaged more and more in waxed paper, for extra protection.

Another leading food use of waxed paper is in the packaging of frozen foods. With the particular problems of frozen foods, such as changes in water content, et cetera, the "ideal" package must have certain characteristics to fully protect the product and prevent foods from spoiling before use. Waxed paper is such an "ideal" package.

Because of its low water vapor and oxygen permeability, waxed paper serves as a backstop against the passage of liquids. It is impermeable to fats and oils, resists acids and other corrosive food components. Moreover, waxed paper keeps frozen foods palatable by excluding foreign odors and preventing the transfer of food flavor.

Perhaps most important from a medical point-of-view, waxed paper prevents light degradation of vitamins and enables frozen foods to be delivered to their ultimate user in the most healthful and health-giving form. Similar advantages accrue in the use of heavily waxed, opaque locker paper for storage of foods in home freezers.

Hospitals and other institutions greatly benefit from the widespread use of waxed paper in packaging food products. In the first place, foods stay fresh longer and there is less spoilage, which holds down operating costs due to food waste. Moreover, waxed paper enables a dietary portion control program that saves money for the hospital and makes for happier, more satisfied patients.

Indeed, hospitals can offer more varied and interesting menus to their patients through tastier, easy-to-prepare foods packaged in waxed paper. The convenience factor, along with elimination of waste and morale-building aspects, all combine to enable the hospital to play its part in healing the sick.

But food use of waxed paper is only one of many ways in which waxed paper is of help to doctors and hospitals in today's modern usage. Other outstanding uses of waxed paper, keyed specifically to the medical profession, will be explored in a second discussion.

Waxed paper, which plays its largest role in today's living as a leading packaging material for bread, cereal, frozen foods and other processed food products, nevertheless has many outstanding modern uses that are keyed specifically to the medical profession.

Doctors and nurses, as well as hospitals themselves, put waxed paper to work for them in many ways. Certain technical qualities and physical properties of waxed paper make it especially useful in the medical field. One example might be its highly waxed finish that prevents other substances from adhering to waxed paper; in fact, waxed paper sticks solely to itself, and then only when it is heat sealed to form a strong bond.

Looking over the field of hospital operations, we find that waxed paper often is used to store the plaster from which casts are made. Similarly, pharmacies, whether or not they actually are located in hospitals, use waxed paper in filling prescriptions. They place it on scales to serve as a base for weighing powders or ointments, and the waxed paper keeps the scale clean. When used as a base under the scale itself, waxed paper serves to keep the counter clean as well.

Surgery in modern-day hospitals also finds a number of uses for waxed paper. It serves as a temporary wrapping for tissues sent from the operating room for testing in the pathology laboratory. Moreover, waxed paper often is used to preserve different kinds of physical specimens, and as a cover for wet gauze.

Wet dressings, whether they are applied in a hospital, the doctor's office or at home, benefit from the use of waxed paper. It holds in the moisture and prevents the bandage from wetting the bed clothes or the patient's clothing. This is the case for such widely divergent undertakings as treatment for burns or wet packs for physical therapy.

Of course, waxed paper plays another role in medication that often is overlooked. Most bandages, surgical dressings and sterilized gauze are packaged in waxed paper by the manufacturer for sanitation and cleanliness. Some doctors even protect their instruments after sterilizing them by covering or wrapping them with waxed paper.

Kitchen uses of waxed paper are limitless, and the busy hospital kitchen preparing meals for hundreds of patients finds waxed paper just as useful as does the housewife making dinner for her family of four. Only the degree is different!

The big advantage that waxed paper offers to hospital kitchens is that it enables them to prepare special diets for patients beforehand and keep the food stored until mealtime distribution. The food remains fresh and flavorful; it is kept completely sanitary. In addition, nourishment "pick-ups" for patients, like glasses of fruit juice, et cetera, can be covered with waxed paper and stacked on trays to be passed out as requested or prescribed.

These are but a few of the ways that waxed paper through its modern usage plays a vital but often unrecognized role in today's medical picture. Waxed paper's versatility and adaptability truly enable it to make a marked contribution to the health and well-being of everyone.

JOHN A. EGAN

THE TUBERCULIN TEST

When Koch announced the discovery of the tubercle bacillus in 1882, the first specific evidence in the diagnosis of tuberculosis became available; namely, the recovery of tubercle bacilli from secreta or excreta of persons who had tuberculosis. The same Koch announced the preparation of the second specific agent in diagnosis; namely, tuberculin, in 1890. He and his immediate disciples first used this substance as a therapeutic and preventive agent for each of which it failed. However, they observed that when introduced into the bodies of persons who had tuberculosis, local, focal and constitutional, reactions occurred which were helpful in diagnosis when this disease was suspected.

Koch introduced tuberculin subcutaneously, but his dosage was so large and reactions often were so severe as to cause harm. Veterinarians in various parts of the world including Leonard Pearson and Charles Cotton of the United States tested large numbers of cattle. At necropsy, lesions were never found in non-reactors, but were nearly always in evidence in reactors, regardless of the previous health status of the animals.

Dr. Talbot Jones, St. Paul, was in Berlin when Koch announced that he had prepared tuberculin. In 1891, Doctor Jones said that the time would probably come when the physician who failed to administer the tuberculin test would lay himself open to just censure.

Apparently, Dr. W. J. Mayo was the first to use tuberculin as a diagnostic agent in Minnesota. In 1894, he said that he had used it when it was difficult to determine the exact nature of disease and had found that it would almost invariably lead to the correct diagnosis. In 1896, Dr. E. J. Davis, St. Paul, stated that tuberculin might do much toward checking the spread of "the great white scourge."

From September to December, 1894, Dr. C. N. Hewitt, Executive Secretary, Minnesota State Board of Health, personally directed tuberculin testing by Dr. Charles E. Cotton of 335 cattle. By December 31 of that year, forty-one of the reactors had been slaughtered and the post-mortem examination sustained the diagnosis. Veterinarians throughout the nation adopted the tuberculin test as their sole diagnostic agent in a national tuberculosis eradication campaign among animals. From 1917 through the fiscal year 1957, veterinarians of the United States alone did post-mortem examinations on 4,062,634 cattle slaughtered because they reacted to tuberculin. This has thoroughly convinced well-informed veterinarians that a characteristic tuberculin reaction practically always means the presence of at least microscopic tuberculous lesions.

Beginning in 1907, Pirquet reported a testing technique which consisted of applying tuberculin to a superficial skin scarification. A year later, Mantoux introduced the intracutaneous method of administration and the same year Lautier reported observations on applying tuberculin directly to unabraded cleansed skin. This method was later revived and is now known as the patch test.

Each of the numerous methods of administration has had its disciples and each one has had its pros and cons. At the present moment, the intracutaneous method (Mantoux) is generally considered to have superiority over the others. This does not mean that other methods are not useful or that they should not be employed when conditions warrant.

From 1908 to 1912, Ghon made meticulous post-mortem examinations of the bodies of 184 children who during life presented no evidence of tuberculosis except the tuberculin reaction. The main object of this study was to determine whether the tuberculin reaction always indicates the presence of tuberculosis. He found the disease in all but one which was not completely examined. When his first examination failed, he took a sec-

ond, and sometimes a third look before finding the lesions because of their minuteness or location. In five of the bodies, the lesions were located extra-thoracicly. Following this, Ghon said, "From the standpoint of the pathological anatomist, my researches, which in regard to the question are not limited to the cases described here, justify me in concurring entirely with those who advocate the specific value of the tuberculin reaction."

There are two tuberculin preparations now in extensive use, namely, Koch's original tuberculin (OT) and purified protein derivative (PPD). From the standpoint of eliciting sensitivity of tissues they are approximately equal. Each has its advantages and disadvantages, but a characteristic reaction from either one indicates the presence of tuberculosis in some stage of its development from microscopic to gross lesions. Therefore a tuberculin reaction justifies the diagnosis of at least the primary type of tuberculosis. From the reaction there is no way of determining, however, whether the reinfection or clinical type of disease has or will develop. If the person who reacts to tuberculin has a clear x-ray film, as is true in most cases on first examination, and has no other evidence of the disease, he should be examined periodically throughout life. This procedure will detect those chronic clinical lesions destined to develop on an average of two or more years before symptoms appear and when treatment is most effective.

Since morbidity and mortality from tuberculosis have so decreased in Minnesota, one frequently hears physicians state that they have not seen a case in a year or more. They are referring to gross lesions detectable by x-ray shadows, et cetera. In all probability such physicians have cases in their offices nearly every day who have earlier stages of the disease which can be detected only by the tuberculin test. Every such person should be advised of this condition so as to be on the alert for possible subsequent clinical disease.

Persons who do not react to tuberculin should have the test repeated periodically at least once a year. The person who has recently become a tuberculin reactor, has usually been in direct contact with a contagious case of tuberculosis since the last negative test. Seeking that contagious case among the adult contacts of the recent tuberculin converter is an excellent case-finding method.

The magnitude of the tuberculosis problem in any family, community, county or state can be determined only by testing all persons with tuberculin. The problem lies among those who react, since each reactor who does not already have clinical disease is a potential case at some subsequent time. Information obtained in Kittson County, Minnesota, is a good example. In 1955 only one person died from tuberculosis in that county and only three new clinical cases were reported. However, when the tuberculin test was offered to the entire citizenry, approximately 2100 reacted. For the most part, these reactors were 40 years of age or older. They were persons who had not been protected against infection during childhood and early adulthood. Among these 2100 persons clinical disease will evolve in a considerable number as the years pass. Similar observations have now been made in several Minnesota counties and municipalities with analogous results, as reported by Jordan and Jordan and Billyeald.

The tuberculin test is the only method by which responsibility can be accurately determined in cases that come to litigation. It is the place where the infection was allowed to occur as indicated by the tuberculin reaction that is responsible rather than the place where the individual happens to be when clinical disease evolves to demonstrable proportions.

Now that antituberculosis drug administration is recommended in many places as soon as possible after tuberculous infection occurs, the importance of periodic tuberculin testing is obvious. In the recent tuberculin converter, lesions are usually still microscopic and vascular so that drugs may be expected to reach all tubercle bacilli. Although present drugs only suppress them, there is hope that a thoroughly germicidal drug will soon become available which will sterilize such lesions. If tuberculosis is not found in this early stage, the lesions may lose their blood supply and there is little likelihood that a germicidal drug in high concentration in the blood stream could reach the bacilli in avascular necrotic areas.

Testing with tuberculin is the best method of disseminating information about tuberculosis that has ever been devised. This applies to the individual, family and the public.

J. A. MYERS, M.D.

President's Letter

A CENTENNIAL YEAR INVITATION CORDIALLY EXTENDED

This is a particular, special personal invitation to all members of the Minnesota State Medical Association to come to the Annual Meeting of the Association. There are changes this year. The meeting is in the last half of the week instead of the first half. There are more symposia and panel discussions. The scientific exhibit is larger than it has ever been. The program is outlined elsewhere in this issue of MINNESOTA MEDICINE.

Because the World Health Organization meets in Minneapolis from May 26 to June 14, 1958, immediately after our meeting, we have been able to devote Friday afternoon to virus diseases and to a report of WHO studies around the world. Dr. Robert Barr has obtained for us Dr. Kleinman from the State Board of Health to discuss current virus disease problems and Dr. Mauricio da Silva of the Pan American Sanitary Bureau to report on immunization with orally administered live virus poliomyelitis vaccine. Dr. da Silva's work was done here and has been continued since he left here. Dr. Fred L. Soper, the director of the Pan American Sanitary Bureau, will discuss these problems. The Pan American Sanitary Bureau is the Western Hemisphere department of the WHO.

The last half of this afternoon will be occupied with World Health Organization Studies and Reports by Dr. Marcolino G. Candau, the Director General of WHO with headquarters in Geneva, Switzerland. The moderator for this session will be Dr. Walter Judd and the discussion will be by Dr. Leroy Burney, Surgeon General of the United States Public Health Service. The principal speaker at the annual banquet will be Dr. David Allman, the President of the American Medical Association.

For three weeks Minneapolis will be literally the public health center of the world. The representatives of 87 countries will be here for the WHO. We who have the good fortune to live in Minnesota have always thought our State to be beautiful and, in many ways, important. Probably we have never even thought of anyone from India, Russia or Africa knowing anything about us. Now we hear that Public Health Officials all over the world are striving for the opportunity to come here. Minneapolis was selected by the WHO for this tenth anniversary meeting partly because the facilities are here, but more, because Minnesota and the midwest are more typical of the real United States than are the large seaboard cities.

We hope that you will come to the 105th annual meeting of the Minnesota State Medical Association and that you will stay for, at least, part of the World Health Organization. We hope that you will meet the visitors from foreign countries and that they will meet you. And we hope our own meeting will be valuable and enjoyable. We hope also that you will listen in on the House of Delegates meetings and that when you leave you will be well informed medically and will know more about the problems facing medicine as a whole.

Horatio B. Sweetser

President, Minnesota State Medical Association

Medical Economics

Edited by the
Committee on Medical Economics,
Minnesota State Medical Association
George Earl, M.D., Chairman

CRUISE DEDUCTIONS QUESTIONED

Recently, a San Francisco Tax Court upheld a Tax Commissioner's action which disallowed 80 per cent of the cost of a physician's cruise, holding that the major portion of the cruise was incurred primarily for a vacation—a non-deductible item.

The cruise sponsored by the American College of Physicians included a series of scientific discussions in addition to sightseeing. The court held that the technical sessions were of short duration.

The proportionate allocation was upheld because the taxpayer physician failed to show how his time was budgeted. Tax authorities did not question the physician's right to deduct the entire cost of attending a convention held prior to the cruise as a business expense.

UNCLE SAM—MEDICALLY SPEAKING

Recently released transcripts of testimony on 1958-59 appropriations for the Department of Health, Education, and Welfare indicate the increasing role of government participation in providing medical care for the American public. Activities included in the hearings are considered vitally important to this nation's practicing physicians. Following are some of the highlights:

Health Insurance

Passage of a law permitting smaller underwriters to pool risks in order to provide coverage for older persons and farm persons is being urged by Secretary of HEW, Marion B. Folsum.

Quackery

The Food and Drug Administration has increased the tempo of its activities to combat the twentieth century methods used by the quack to bilk millions of dollars from the American people by fraudulent means.

Disability Benefits

Approximately 160,000 persons have taken advantage of Social Security disability cash benefits during the first six months of the program's existence. Five-month medical determinations of disability have been cut to three. More than $2 million will be spent in the year beginning July 1, 1958, for purposes of examining applicants for disability benefits.

Illicit Drug Sales

Certain Texas and Georgia physicians have been under fire from Federal Authorities for dispensing abnormally large quantities of amphetamines. The report cited one case where an under cover agent purchased 55,000 tablets from one doctor over a period of twenty-eight days.

Hospital Construction

House approval of more than the $75 million requested by President Eisenhower for Hill-Burton grants in aid to help finance construction and improvement of hospitals throughout the country is expected to receive favorable attention.

THIS MATTER OF GIVING

Americans give an estimated annual $6 billion to charitable and religious organizations. Some would say this is but a fraction of what Americans could give if they but would.

All about us are evidences of benefits derived through American benevolence. Conversely, there are untold instances of the marks of the charitable charlatan. Giving ought to be a personal matter—not brought about by habit or high pressure.

Who should receive how much and for what purpose should be individually determined.

When in question about the good intentions of a potential recipient, check with the local Community Chest, Better Business Bureau, Health Agencies, Chamber of Commerce, Bankers or local Clergy representatives.

When you wish to give:

1. Give only after you investigate the cause, the sponsor and the purpose for which the funds will be spent.
2. Give objectively—don't allow yourself to become carried away by an emotional "pitch."
3. Give only after you are able to identify patrons of the drive. "Director," "Coordinator," "Civic Leader" and other impressive titles can throw a left curve.

4. Give only if a telephone solicitor will fully identify himself, presenting all the facts.

5. Give only when a solicitor doesn't mind receiving your check via U. S. mail. Be on guard when a cash donation is requested.

6. Give only to street solicitors with cup, container or coin bank, when they represent an accepted cause.

7. Give only if the cause is recognized by the state law.

8. Give out of the goodness of your heart. Don't let friends or acquaintances apply "gentle pressure."

AMA PRESIDENT LAUNCHES ASSAULT ON FORAND BILL

A letter from the AMA President, Dr. David Allman, to approximately 140,000 doctors has urged a gross-root offensive to insure defeat of the Forand Bill. The letter urging defeat of the successor to the Wagner-Murray-Dingell Bill was brought to the attention of doctors at a time when congressmen and senators were home during the Easter holiday, sounding out public opinion.

Minnesota Representative, John A. Blatnik, is the latest to join the Democratic bloc of co-sponsors of the Forand Bill.

Senator Wayne Morse, Democrat from Oregon, recently made a floor speech urging enactment of Companion Bill (S-3508) to the Forand Bill.

"I want to express my personal thanks and appreciation," said Senator Morse, "to Mr. Forand for his leadership on this matter. I am happy to acknowledge that I have simply followed his lead by incorporating into my bill the health insurance program he had first introduced in HR 9467.

"I hope that, by so doing, I can reenforce the chances that a health insurance program will soon be adopted," stated Senator Morse.

Senator Morse's bill would amend the Social Security act (a) to provide hospital and nursing home care and surgical benefits identical with those in the Forand bill, (b) to increase the wage base and rate for social security payroll taxes and (c) to increase social security benefits. By substituting a table for the present law's formula to determine benefits, this bill would increase the minimum to $40 per month, the maximum family benefit from $200 to $346.40, and the maximum individual primary benefit from the present $108.50 to $173.20. Also, a more liberal "drop out period" would be provided. The wage base on which tax is levied would be increased from the present $4,200 to $6,000, and the rate increased to 3½ per cent for employer and employee and 5¼ per cent for self-employed for the 1959-60 period. By 1975, the respective rates would be 5½ per cent and 8¼ per cent. The bill also would increase U. S. public assistance payments by 25 per cent.

WELFARE BILLS CONCERNING THE AGED

In addition, the House Education and Labor Committee has conducted hearings on eighteen bills dealing with welfare of the aged.

Worth noting are bills sponsored by Representative Edith Green (D., Oregon) and John E. Fogarty (D., R. I.). Mrs. Green not only indorsed Forand bill but said legislation that would go further is needed. She states Government should make provision for defraying medical expenses of elderly persons who are *not* eligible for such protection under old age and survivors insurance. She also urged consideration be given the establishment of a separate institute on geriatrics in National Institutes of Health.

Her bill, along with ten other pending bills, would set up a bureau of Older Persons in Department of HEW. The Fogarty bill (HR 9822) proposes a White House conference on Aging, to be preceded by warmup conferences in the several states.

HEW SPENDING URGED

Government spending for medical research facilities, hospitals and water treatment plants from now to the end of the fiscal year ending June 30 are expected to exceed $800 million. Originally, appropriations for this purpose had been pared to $670 million. The increased spending by the Department of Health, Education and Welfare is an anti-recession measure designated to stimulate business activity.

Largest increase is in the building of medical research facilities by hospitals, medical schools and other institutions, for which the U. S. provides $30 million a year. Total value of contracts to be let in the period has been increased from an estimated $120 million to $182 million. Hospital contracts to be let under Hill-Burton will total $405 million, rather than the originally planned

$381 million, and sewage plant contracts will move up from $170 million to $215 million. In all cases, totals include local as well as U. S. money.

Rural Clinics Grants.—Senators Payne (R., Me.) and Flanders (R., Vt.) are sponsoring an amendment to Hill-Burton to allow private, non-profit associations or corporations to get up to $25,000 in federal funds on a matching basis for building and equipping diagnostic and treatment centers. Rural communities with population up to 15,000 would be eligible and the group need not be affiliated with a hospital as required for other Hill-Burton projects. This bill *(S. 3588)* was followed by one from Rep. Coffin (D., Me.) along similar lines. His bill, H.R. 11826, offers grants to a single town of not over 10,000 or a group of towns with no more than 15,000. One major difference with the Payne-Flanders bill is that in *H.R. 11826* the association or corporation would have to have a formal affiliation with a non-profit teaching hospital.

RECOMMENDATION FOR NURSING HOMES AND HOMES FOR THE AGED

Thousands of old people are not receiving even routine medical supervision in many of this nation's rest homes, much less, the benefits of recent advances in medicine of special value for severely handicapped patients. Secretary of Health, Education and Welfare, Marion B. Folsom, recently told representatives of approximately 150 individual homes, social service agencies, State Health and Welfare Departments and delegates from 32 national organizations. Twenty-eight states were represented. Secretary Folsom's remarks were made on the occasion of the first National conference on nursing homes and homes for the aged, which was held recently in Washington, D. C.

Surgeon General Leroy E. Burney stressed the lack of high-quality institutions in his address of thousands of older patients in general hospitals for longer than necessary, and deprives hundreds of thousands of other individuals of good care.

However, Dr. Burney emphasized, many institutions have demonstrated that the same great advances in medicine, psychiatry, sociology, architecture, construction, equipment and personal services which revolutionized the community general hospital are applicable to the nursing home and home for the aged. He said the main task of the Conference was to find ways that will enable all such institutions to achieve comparable results.

Following are facts about nursing homes and homes for the aged in the United States:

In the United States, there are about 25,000 nursing homes, with 450,000 beds. Of these beds, 180,000 are in "skilled nursing" homes and 80,000 in homes that provide skilled nursing care.

Eighty years is the average age of persons living in nursing homes. Two-thirds of them are over seventy-five years old, and two-thirds are women. Less than half can walk alone. More than half are disoriented at times. About half are incontinent, and two-thirds have some type of circulatory disorder.

Only 3 per cent of nursing homes are publicly owned. Seventy-one per cent of the beds are in private homes and 15 per cent in publicly owned homes. Privately owned nursing homes average about eighteen beds in size. Publicly owned homes are bigger, averaging about sixty-nine beds.

The average monthly charge for nursing homes care is $150. In thirteen states studied, the average cost of nursing home care was from $90 to $200 per month. Public funds pay for about half the people in nursing homes. Public assistance payments are from $55 to $155 per month.

Every state and territory, except the Virgin Islands and Puerto Rico, licenses nursing homes. Homes for the aged are licensed except in South Carolina, the Virgin Islands and Puerto Rico.

Responsibility for licensure is as follows:

	Nursing Homes	*Homes for the Aged*
State Health Dept's	42	34
State Welfare Dept's	6	14
Other State Agencies	3	2
None	2	3
TOTAL	53	53

Council for Health Care of the Aged Formed

The American Dental Association, the American Hospital Association, the American Medical Association, and the American Nursing Home Association have announced the establishment of the Joint Council to Improve the Health Care of the Aged.

Objectives of the council, the formation of which has been under consideration for some time

by the sponsoring groups, are: (1) to identify and analyze the health needs of the aged; (2) to appraise available health resources for the aged; (3) to develop programs to foster the best possible health care for the aged regardless of their economic status.

The Joint Council to Improve the Health Care of the Aged is made up of three representatives of each sponsoring organization. One of the first jobs of the council will be to determine exactly what are the health problems of the aged.

The need for new programs in this field is accented by the fact that the life expectancy of individuals has been constantly increasing in recent years. In 1935, life expectancy in the United States was an average sixty years. The most recent figure indicates the average life expectancy now to be seventy years.

One of the principal immediate projects of the council will be the development of programs and facilities to be tailored to the health needs and finances of the aged.

Another facet of the council's broad-range program will be to work closely with health insurance groups in an effort to improve the coverage of the aged and to see that their insurance dollars go further.

It is the belief of the Joint Council to Improve the Health Care of the Aged that much can be done for older people by the states and communities, and the council will endeavor to stimulate the activities at these levels of government.

Special research projects contemplated by each of the organizations supporting the council will be pooled and programs developed to meet the health needs of the aged. The ultimate goal is to provide adequate health care at reasonable costs.

GOVERNMENT-SUPPORTED COLLEGE RESEARCH

Almost two-thirds of all money for research and development work at colleges and universities in the United States is allocated by the Federal Government according to a National Science Foundation survey. The extent of United States Government participation amounts to about $500 million. Most of the funds are earmarked for defense or similar projects.

PANCREAS AND DIABETES MELLITUS IN MAN AND ANIMALS

(Continued from Page 346)

hypoglycemic sulfonylureas in the treatment of diabetes in man—a comparison. Canad. M.A.J., 74: 968-972, 1956.

19. Wrenshall, G. A., Best, C. H., and Hartroft, W. S.: Factors influencing the amount of insulin extractable from beef pancreas I. Effects of aging fresh pancreas at room temperature. Canad. J. Biochem. & Physiol., 35:527-535, 1957.
20. Wrenshall, G. A., Bogoch, A., and Ritchie, R. C.: Extractable insulin of pancreas: correlation with pathological and clinical findings in diabetic and nondiabetic cases. Diabetes, 1:87-107,1952.
21. Wrenshall, G. A., Casselman, W. G. B., and Best, C. H.: Factors influencing the amount of insulin extractable from beef pancreas III. Effects of temperature and of freezing and thawing on changes accompanying the aging of fresh pancreas. Canad. J. Biochem. & Physiol., 35:545-548, 1957.
22. Wrenshall, G. A., Collins-Williams, Jean, and Hartroft, W. S.: Incidence, control and regression of diabetic symptoms in the alloxan-treated rat. Am. J. Physiol., 156:100-113, 1949.
23. Wrenshall, G. A., and Hamilton, J. D.: Sex differences in the amount of insulin extractable from diabetic human pancreas. Ann. New York Acad. Sc., 71:154-163, 1957.
24. Wrenshall, G. A., Hartroft, W. S., and Best, C. H.: Insulin extractable from the pancreas and islet cell histology: comparative studies in spontaneous diabetes in dogs and human subjects. Diabetes, 3:444-452, 1954.

RUPTURE OF VAGINAL VARICOSITIES

(Continued from Page 347)

Observations

1. This case points out the importance of routine presurgical vaginal (manual and speculum) examinations on contemplated emergency Cesarian sections.

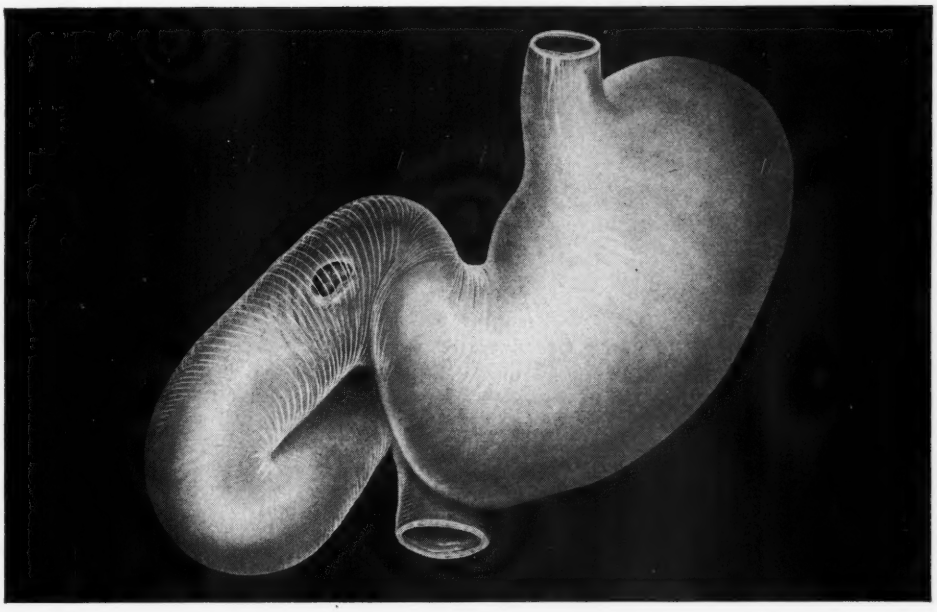
(a) In an emergency such as this, a Cesarian section might have been done in haste, on the presumptive diagnosis of placenta previa, with possible maternal exsanguination during the procedure at worst, and, at least, a resultant premature child, less qualified for survival.

(b) Vaginal examination may supplant, augment, or corroborate the results of x-ray in cases where shock is impending and definitive diagnostic measures are limited by the extremity of the patient's condition.

2. This case again stresses the important fact that there are causes of severe antepartum bleeding in addition to placental abnormalities.

3. A third point is that conditions not present in early pregnancy may develop at any time and cause complications in the last trimester.

CONFIRMED THERAPEUTIC UTILITY



Pro-Banthine® "proved almost invariably effective in the relief of ulcer pain,

*in depressing gastric secretory volume and in inhibiting gastrointestinal motility."**

"Our findings were documented by an intensive and personal observation of these patients over a 2-year period in private practice, and in two large hospital clinics with close supervision and satisfactory follow-up studies."*

Among the many clinical indications for Pro-Banthine (brand of propantheline bromide), peptic ulcer is primary. During treatment, Pro-Banthine has been shown repeatedly to be a most valuable agent when used in conjunction with diet, antacids and essential psychotherapy.

Therapeutic utility and effectiveness of Pro-Banthine in the treatment of peptic ulcer are repeatedly referred to in the recent medical literature.

Pro-Banthine Dosage

The average adult oral dosage of Pro-Banthine is one tablet (15 mg.) with meals and two tablets at bedtime.

G. D. Searle & Co., Chicago 80, Illinois. Research in the Service of Medicine.

---

*Lichstein, J.; Morehouse, M. G., and Osmon, K. L.: Pro-Banthine in the Treatment of Peptic Ulcer. A Clinical Evaluation with Gastric Secretory, Motility and Gastroscopic Studies. Report of 60 Cases, Am. J. M. Sc. *232*:156 (Aug.) 1956.

SEARLE

BLUE SHIELD-BLUE CROSS

Increased incidence and increased utilization of the Blue Shield contract by participant subscribers during the year 1957 as compared to 1956 is shown by a comparison of the number of services of physicians provided Blue Shield benefits per year per 1,000 contracts and per year per 1,000 subscribers.

During 1957, Blue Shield provided benefits for 963 physicans' services per 1,000 contracts, or 362 services for 1,000 participant subscribers. In the previous year, 1956, Blue Shield benefits were provided for 859 services of physicians per 1,000 contracts, and 323 services per 1,000 subscribers.

The 1957 ratio of physicians' services provided Blue Shield benefits per 1,000 contracts and subscribers shows an average of almost one service for each contract in effect and over one service for every three participant subscribers.

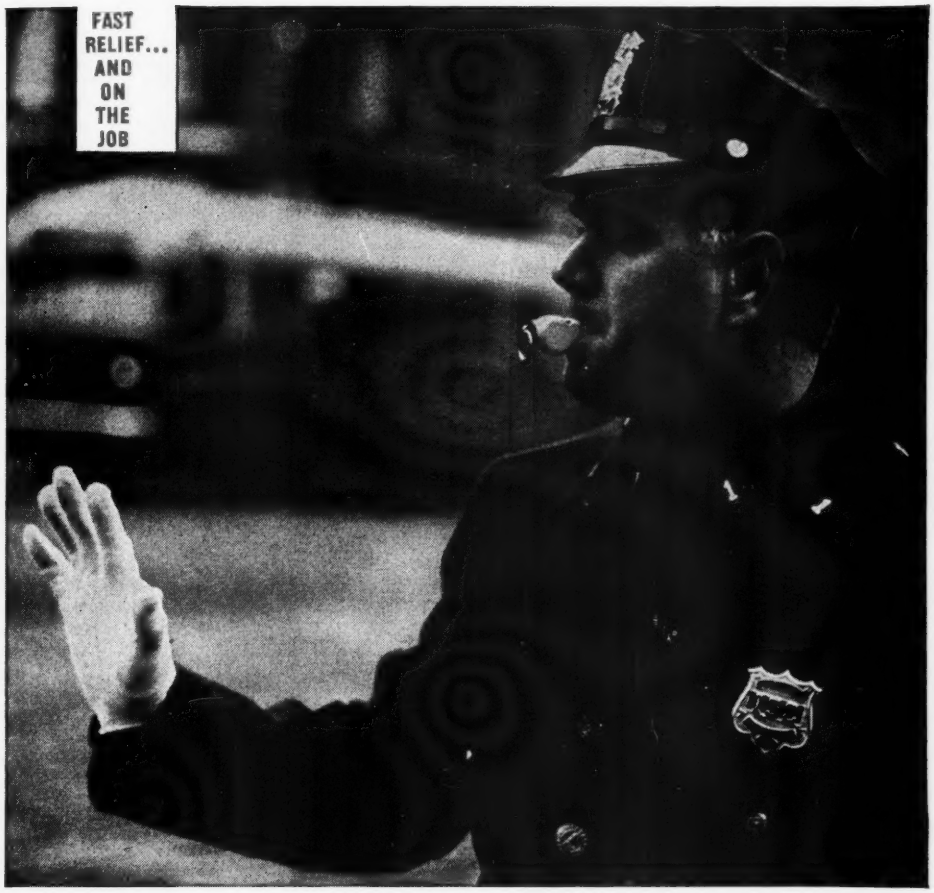
Percentagewise, the increase in the number of doctors' services provided Blue Shield benefits per 1,000 subscribers and per 1,000 contracts in 1957 over 1956 is approximately 12 per cent. This percentage increase clearly illustrates the increased incidence and utilization experienced by Blue Shield in 1957 over 1956.

During 1957, a total of 307,171 services of doctors were provided Blue Shield benefits, while during 1956, Blue Shield provided benefits for 250,600 physicians' services rendered subscribers. The number of services for which Blue Shield provided benefits in 1957 is approximately 22 per cent greater than the number of services provided benefits during 1956.

Blue Cross subscriber usage of benefits is continuing at the high rate experienced during the last quarter of 1957. During the first two months of 1958, the 35,080 subscribers hospitalized represented 495 cases paid per year per 1,000 contracts protected, an increase of 3.8 per cent over the 477 cases experienced during the similar period of 1957.

The major portion of this increased usage, 83.3 per cent, is attributable to the increase in number of Blue Cross subscribers receiving hospital care for accidental injuries and poisonings. During the first two months of 1958, 6,257 subscribers representing 17.8 per cent of all Blue Cross cases paid received hospital care because of accidental injuries. During the same period of the previous year, 5,058 subscribers or 15.3 per cent of total cases paid were hospitalized due to accidental injuries. Blue Cross benefits for treatment of accidents incurred by subscribers averaged over $200,000 per month during the first two months of the year. Annually this would amount to $2,400,000 of Blue Cross benefits—or over $2 per person; man, woman and child, covered by Blue Cross in Minnesota—for hospital treatment of accidental injuries and poisonings.

The frequency of diseases of the digestive system incurred by Blue Cross subscribers to date this year as compared to the same period of 1957 is the second leading reason for increased usage of Blue Cross benefits during this period. During the first two months of 1958 over $900,000 in benefits has been provided 4,754 subscribers hospitalized because of diseases of the digestive system compared to approximately $780,000 in benefits provided 4,415 subscribers during the same period of 1957.



IN ALL DIARRHEAS . . . REGARDLESS OF ETIOLOGY

comprehensive control with **CREMOMYCIN**®

SULFASUXIDINE* PECTIN-KAOLIN-NEOMYCIN SUSPENSION

SOOTHING ACTION . . . Kaolin and pectin coat and soothe the inflamed mucosa, adsorb toxins and help reduce intestinal hypermotility.

BROAD THERAPY . . . The combined antibacterial effectiveness of neomycin and Sulfasuxidine is concentrated in the bowel since the absorption of both agents is negligible.

LOCAL IRRITATION IS REDUCED and control is instituted against spread of infective organisms and loss of body fluid.

PALATABLE creamy pink, fruit-flavored CREMOMYCIN is pleasant tasting, readily accepted by patients of all ages.

*Sulfasuxidine is a trade-mark of Merck & Co., Inc.

MSD **MERCK SHARP & DOHME**
DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

Meetings and Announcements

STATE

MINNESOTA STATE MEDICAL ASSOCIATION, 105th annual meeting, Minneapolis, May 22, 23 and 24, 1958. Business sessions and exhibits, Minneapolis Auditorium. Headquarters, Leamington Hotel.

NATIONAL

American Congress of Physical Medicine and Rehabilitation, 36th annual scientific and clinical session, Bellevue-Stratford Hotel, Philadelphia, August 24-29, 1958.

American Gastroenterological Association, 59th annual meeting, Washington, D. C., May 30-31, 1958. H. M. Pollard, M.D., Secretary-General, University Hospital, Ann Arbor, Michigan.

American Goiter Association, 1958 meeting, June 17-19, San Francisco, California.

Gerontological Society, Inc., Bellevue Stratford Hotel, eleventh annual scientific meeting, Philadelphia, Pennsylvania, November 6, 7, and 8, 1958.

Trudeau School of Tuberculosis and Other Pulmonary Diseases, forty-third session, Saranac Lake, N. Y., June 2 to 20, 1958. Detailed information may be obtained from the Secretary, Trudeau School of Tuberculosis and Other Pulmonary Diseases, Box 500 Saranac Lake, N. Y.

INTERNATIONAL

Fifth International Congress on Diseases of the Chest, sponsored by American College of Chest Physicians, Tokyo, Japan, September 7-11, 1958.

Third International Congress of Allergy, sponsored by International Association of Allergology and French Allergy, Association, Paris, France, October 19-26, 1958.

World Congress of Gastroenterology, Washington, D. C., May 24-31, 1958. Joint meeting with the American Gastroenterological Association, Dr. H. M. Pollard, Secretary-General, University Hospital, Ann Arbor, Michigan.

World Health Organization. Municipal Auditorium, Minneapolis, Minnesota, May 26-June 14, 1958.

STATE MEETING HAS CENTENNIAL "WHO" FLAVOR

The 105th annual meeting of the Minnesota State Medical Association will be held May 22, 23, and 24 in the Minneapolis Auditorium with headquarters in the Hotel Leamington. Association members are asked to note the change from a "week end" to a "middle of the week" opening day.

Delegates from eighty-eight nations of WHO, including the Minister of National Director of Health from each nation are expected to attend. Invitations have been extended to WHO visitors to participate in the various centennial program activities of the Minnesota State Medical Association. The program committee for the annual meeting has been fortunate in securing a varied program of speakers representing world renowned men from the areas of medical science, medical economics and world health.

A representative sampling from the speakers program includes: Mauicio M. da Silva, M.D., Pan American Sanitary Bureau, Washington, D.C.; Fred L. Soper, M.D., Director, Pan American Sanitary Bureau, Washington, D. C.; Leroy E. Burney, M.D., Surgeon General, Public Health Service, Washington, D. C.; Marcolino G. Candau, M.D., Director-General, WHO; David B. Allman, President, AMA; William Menninger, M.D., President, Menninger Foundation, Topeka, Kansas.

The opening meeting of the house of delegates will convene Wednesday, May 21, at 2 p.m., a change from the week end opening sessions of the past.

Dr. David B. Allman, President of the American Medical Association. will be speaker at the annual banquet Friday, May 23, at 7 p.m. in the Hall of States, Hotel Leamington. Fifty Club certificates, Southern Minnesota Medical Association Medal, and Distinguished Service Award presentations will be made in conjunction with the banquet.

Open house will be held Thursday, May 22, at 9 p.m. in the Hall of States, Leamington Hotel. Members of the Hennepin County Medical Society will be hosts for the occasion.

Committee breakfasts will be held Thursday and Friday mornings, May 22 and 23, at 8:00 a.m.

The dinner for new members and county officers will be held at 6 p.m., May 21, Town Hall, Hotel Leamington.

The scientfiic program sessions will include panel discussions on the following topics: Emergencies; The Family Doctor's Responsibility to His Pre-School Eye Patient; What's New in Dermatology; Surgery; Viruses and Virus Diseases; Mental Health; Medico-Legal Aspects of Heart Disease.

Lectures to be presented include: Arthur H. Sanford Lecture in Clinical Pathology, Minnesota Division of the American Cancer Society Lecture, Russell D. Carman Memorial Lecture and Northwestern Pediatric Society Lecture.

Specialty groups which have accepted dinners or luncheons during the annual meeting include Academy of General Practice, Medical Women's Association, Minnesota Academy of Ophthalmology and Otolaryngology, Radiological Society of North America, and Society of Clinical Pathologists.

For the sportsminded, the annual trap and skeet shoot will be held Saturday, May 24, from 11 a.m. to 4 p.m. at the Twin City Hopkins Gun Club. Dinner, to which wives are invited, will be served at the Edina Country Club at 6:30 p.m.

Golfers will be able to catch up on their favorite

(Continued on Page A-46)

MY DAD— HE HURT HIS BACK REAL BAD

"It happened at work while he was putting oil in something"

"He told Mom his shoulder felt like it was on fire"

"He couldn't swing a bat without hurting"

"But Doctor gave him some nice pills--and the pain went away fast"

"Dad said we'd play ball again tomorrow when he comes home"

AND THE PAIN WENT AWAY FAST

FOR PAIN

Percodan®

(Salts of Dihydrohydroxycodeinone and Homatropine, plus APC) **TABLETS**

ACTS FASTER...
usually within 5-15 minutes

LASTS LONGER...
usually for 6 hours or more

MORE THOROUGH RELIEF...
permits uninterrupted sleep through the night

RARELY CONSTIPATES...
excellent for chronic or bedridden patients

and now... **NEW**

Percodan®-Demi

VERSATILE

New "demi" strength permits dosage flexibility to meet each patient's specific needs. PERCODAN-DEMI provides the PERCODAN formula with one-half the amount of salts of dihydrohydroxycodeinone and homatropine.

AVERAGE ADULT DOSE: 1 tablet every 6 hours. May be habit-forming. Available through all pharmacies.

Each PERCODAN-Tablet contains 4.50 mg. dihydrohydroxycodeinone hydrochloride, 0.38 mg. dihydrohydroxycodeinone terephthalate, 0.38 mg. homatropine terephthalate, 224 mg. acetylsalicylic acid, 160 mg. phenacetin, and 32 mg. caffeine.

Literature? Write

Endo® **ENDO LABORATORIES**
Richmond Hill 18, New York

U.S. Pat. 2,628,185

STATE MEETING HAS CENTENNIAL FLAVOR

(Continued from Page A-44)

pastime Wednesday, May 21, from 11 a.m. to 1 p.m. at the Edina Country Club. A dinner for physician golfers and their wives will be served at 6:30 p.m.

Official programs will be mailed to all members. Reservation blanks for those activities requiring advance reservation will be enclosed with the program, for the convenience of those planning to attend.

POSTGRADUATE REFRESHER COURSE IN HAWAII

From August 5 to August 21, 1958, the University of Southern California School of Medicine will hold a postgraduate course in Honolulu and on board the S.S. Matsonia. The course will center around actual case histories, which will be used to emphasize diagnostic and therapeutic features.

Price range from $382.15 to $657.25, plus tuition $125.00.

Information concerning this course may be obtained from the Director of the Postgraduate Division, USC School of Medicine, 2025 Zonal Avenue, Los Angeles 33, California.

CERVICAL SMEAR PROGRAM SPEAKERS AVAILABLE

The Professional Education Committee of the American Cancer Society, Minnesota Division, in an effort to co-ordinate the state-wide adoption of Cervical Smear Programs is eager to provide speakers to the various county medical societies or better yet to the group medical societies for the purposes of acquainting the medical group with the most recent information on this procedure as well as the more practical aspects of how the tests should be performed and the follow-up recommendations. Secretaries of those groups interested in speakers should contact Mr. Allan Stone, Executive Secretary, American Cancer Society, 3702 East Lake Street, Minneapolis 6, Minnesota.

AMERICAN HEART ASSOCIATION PAPERS REQUESTED

The American Heart Association will hold its thirty-first annual scientific sessions, October 24-26, 1958, in San Francisco, California.

Applications for presentation of papers at the 1958 Scientific Sessions may be obtained from Dr. F. J. Lewy, Assistant Medical Director, American Heart Association, 44 E. 23rd Street, New York 10, New York. Abstracts must be submitted before June 13, 1958.

PSYCHIATRY FELLOWSHIP TO CONTINUE

The American Psychiatric Association has announced a $100,000 grant from the Smith, Kline & French Foundation to continue the Foundation's fellowships in Psychiatry through 1960.

Seven main types of Smith, Kline & French Foundation Fellowships are available: "A"—support for advanced training of full-time staff psychiatrists of public mental hospitals and schools for the retarded; "B"—awards to hospitals for visiting lectureships and for teaching fellowships; "C"—support to medical schools, teaching centers, et cetera, for extension training programs; "D"—student fellowships to encourage talented medical students to broaden their experience in psychiatric approaches and practice; "E"—medical fellowships to encourage broadened skill in the handling of psychiatric problems by physicians other than psychiatrists; "F"—foreign scholar lectureships to bring outstanding men to the United States; "G"—residency training fellowships under unusual circumstances.

Applications for consideration in May and October must be received by the Fellowship Committee by April 1 and September 15. Information and application forms may be obtained from the Committee, Box 7929, Philadelphia.

CARDIOVASCULAR FELLOWSHIPS AVAILABLE

The Minnesota Heart Association has invited applications for research fellowships and research grants for the fiscal year beginning September 1. All areas of cardiovascular disease study will be considered.

Grants are to be allocated from public contributions to the 1958 Heart Fund drive.

Requests from qualified persons must be submitted to the Association office, 1821 University Avenue, Saint Paul 4, Minnesota, by May 15, 1958. Application forms can be obtained from the Minnesota Heart Association.

POSTGRADUATE COURSES ANNOUNCED

"The Physiological Basis of Clinical Electrocardiography" is offered by the New York University Post-Graduate Medical School during the week of June 2 through 6. Tuition $75.00.

Occupational Medicine, an eight week full-time course for practicing physicians, will be given September 15 through November 7, 1958.

Information may be obtained through the office of the Associate Dean, New York University Postgraduate Medical School, 550 First Avenue, New York 16, N. Y.

PUBLIC HEALTH INFORMATION

Six hundred dailies, weeklies, radio and TV stations in Minnesota now receive the "How's Your Health?" feature each week. The articles compiled by the public relations department of the Minnesota State Medical Association feature timely health topics. All Minnesota newspaper editors regularly receive "How's Your Health?" as a part of their weekly Minnesota Editorial Association mailing. Members are urged to encourage editors who do not use the feature to do so. Similarly, a compliment to editors who publish "How's Your Health?" might be good public relations on the local level.

Ten 20-second sound-on-film health jingles have been placed in the film libraries of the eight Minnesota commercial TV stations. The spots are based on well-known nursery rhymes.

Stations which have received the jingles to be used on a Public Service basis include: WCCO-TV, KSTP-TV, WTCN-TV and KMGM-TV in the Twin Cities; WDSM-TV and KDAL-TV in Duluth; KROC-TV in Rochester and KMMT-TV in Austin.

"Doctor Tell Me," the Minnesota State Medical Association radio health program, is now heard on twenty-two Minnesota radio stations.

Woman's Auxiliary

COUNTY AUXILIARY NEWS

McLeod County

On Wednesday, March 19, the Woman's Auxiliary to the McLeod County Medical Society honored Mrs. C. L. Oppegaard, Crookston, president, and Mrs. Reuben Erickson, Minneapolis, president-elect of the Minnesota Woman's Auxiliary, with a luncheon at Bob's Supper Club in Hutchinson. The occasion celebrated the tenth anniversary of the organization of the McLeod County unit.

Of the thirteen charter members, eight are still active in the present membership of eighteen. The group's first president was Mrs. A. M. Jensen of Brownton. Successive presidents were: Mrs. A. Neumaier, Glencoe; Mrs. D. Brink, Hutchinson; Mrs. J. D. Selmo, Norwood; Mrs. J. J. Smyth, Lester Prairie; Mrs. E. W. Lippmann, Hutchinson; Mrs. K. Peterson, Hutchinson; Mrs. Chas. Sheppard, Hutchinson; Mrs. C. W. Truesdale, Glencoe; and Mrs. M. M. Howell, Glencoe.

Guests included thirty Auxiliary members from seven surrounding counties. Bob's Supper Club had been transformed into a spring garden by the decoration committee, Mrs. Carl Bretzke and Mrs. George Smith of Hutchinson. Tickets chairman was Mrs. A. M. Jensen, Brownton. Mrs. C. W. Truesdale, Glencoe, Mrs. J. J. Smith, Lester Prairie, and Mrs. J. D. Selmo, Norwood, comprised the arrangements committee, and Mrs. Chas. Sheppard, Hutchinson, was the hospitality chairman.

Mrs. M. M. Howell, Glencoe, president, presided. The speakers' table was decorated with old fashioned bouquets of tulips, daffodils and hyacinths, centered with an arrangement of spring flowers in a straw hat. Mrs. Oppegaard addressed the group on "The Role of the Woman's Auxiliary." Mrs. Erickson outlined the plans of the forthcoming WHO convention to be held in Minneapolis in the early summer. The group enjoyed a discourse on "Where Did You Get That Hat?" given by Mrs. E. J. Gavin of Glencoe, highlighted by her display of hats and points on making them.

Following the meeting Mrs. Oppegaard and Mrs. Erickson drove to Redwood Falls to attend a regional meeting of the Auxiliary.

Ramsey County

Instead of the regular February luncheon meeting, the Ramsey County Auxiliary attended area meetings in the homes of members. These coffee parties were arranged by Mrs. Wallace Gleason and Mrs. Malcolm Pearson, co-chairmen.

In March, members were guests of the Auxiliary at a luncheon and style show at the Saint Paul Women's City Club. Mrs. Dorothy Krebs of Frank Murphy's presented a collection of hats which were modeled by members. "Millinery Memories" was the title of the Vivien Grace Gibson collection of antique hats shown by Mrs. Curtiss Oberg. The program was planned by Mrs. John Meade and Mrs. Burtis Mears.

Mrs. Donald Derauf, legislation chairman, prepared a report on pertinent bills in Congress—the Forand and the Jenkins-Keogh bills. Mrs. Rodney Sturley, introduced by Mrs. Herman Wolff, president, presented a paper.

Tribute was paid to the memory of Mrs. A. E. Nichols, who served as president of the Auxiliary during the 1938-39 period.

A letter from a University medical student, thanking the Auxiliary for a $200 scholarship he had received from the Auxiliary, was read.

The Auxiliary assisted Ramsey County Medical Society in publicizing a high school essay contest on "The Advantages of Private Practice in Medicine." Dr. Francis Lynch presented the monetary awards, which had been donated by the Medical Society, to the winners.

Zumbro Valley Auxiliary

The March meeting of the Zumbro Valley Medical Auxiliary was held on Wednesday, March 12, at 2:30 P.M. at the Mayo Foundation House.

Tea was served, followed by a business meeting. A film on Traffic Safety, sponsored by the AAA was then shown.

REMINDERS ABOUT THE 36TH ANNUAL MEETING

Thursday, May 22

Registration—8:30 a.m.
Executive Board Meeting—9:45 a.m.
Executive Board Luncheon—12:15 p.m.
Hennepin County Historical Society Tour—2:30 p.m.
Tea—3:00 p.m.
Open House—9:00 p.m.

Friday, May 23

Registration—8:30 a.m.
Annual Meeting—9:30 a.m.
Annual Luncheon—1:00 p.m.
Post-Convention Board Meeting—3:30 p.m.
Annual Banquet—7:00 p.m.

An official program will be mailed at an early date. In addition, a preliminary program of Woman's Auxiliary activities appears in the April issue of this publication. Remember to make all necessary reservations early. Need more be said?

HEALTH CAREERS FILM PREVIEW

"Helping Hands for Julie" is the title of a new health careers film, co-sponsored by the American Medical Association and the American Hospital Association, under a grant from E. R. Squibb and Sons.

This film is to be completed and ready for previewing during National Hospital Week, May 11 to 17, for the exclusive purpose of advance showings to vocational guidance counselors.

County Auxiliary officers may wish to contact local hospitals to offer co-operation in the sponsorship of this film.

The Woman's Auxiliary is sponsoring a special show-

(Continued on Page A-56)

General Interest

Dr. Charles C. Cooper, Saint Paul, was named vice president of the American Academy of General Practice at its meeting in Dallas.

* * *

Dr. Harry M. Weber, head of the section of diagnostic roentgenology at the Mayo Clinic, delivered the Fred Jenner Hodges lecture on radiology April 11 at the University of Michigan.

* * *

Dr. Stanley Karansky, a member of the section of anesthesiology of the Mayo Clinic since 1955, has left Rochester for Phoenix, Arizona, where he will carry on a private practice of anesthesiology.

* * *

Two Mayo Clinic staff men were on the speaking program of the sectional meeting of the American College of Surgeons in Salt Lake City. **Dr. John C. Ivins** participated in a symposium on trauma and **Dr. Thomas T. Myers** participated in a panel on peripheral vascular disease.

* * *

Dr. J. Arnold Bargen, chairman of the section of gastroenterology in the Mayo Clinic, and professor of medicine in the Mayo Foundation, has been appointed to the medical advisory board of the National Foundation for Research in Ulcerative Colitis, of Washington, D. C.

* * *

Two University of Minnesota medical professors have won Purdue Frederick medical achievement travel awards to enable them to attend medical meetings of their choice in the United States and Europe.

They are **Dr. C. Walton Lillehei**, professor of surgery in the school of medicine and originator of the world-famed cross-circulation "open heart" surgery technique, and **Dr. Edgar V. Allen**, professor of medicine at the Mayo Foundation graduate school, Rochester, Minnesota, and a specialist in cardiovascular disease.

The awards are presented by the Purdue Frederick Company, pharmaceutical firm, through the International Council for Health and Travel.

* * *

Dr. Harry B. Hall has been elected chief of staff at Fairview Hospital. Other officers for 1958-59 are **Drs. C. Gordon Watson**, chief-elect; **Kristofer Hagen**, secretary, and **Dale H. Correa**, treasurer.

Doctors attending the annual staff meeting heard Dr. Robert Meller, psychiatric committeechairman, report on the first six months operation of the hospital's 34-bed psychiatric ward.

* * *

Dr. Donald T. Cundy has announced the opening of a new office at 697 Marquette Bank Building in Minneapolis.

* * *

A foursome from Rochester recently left for Europe, where they spent two weeks. **Dr. John Kirklin** and **Dr. Robert Patrick** of the Mayo Clinic and their wives spent a week in Germany and a week in England.

The doctors attended a medical meeting in Munich, Germany, where they both presented papers. Dr. Kirklin also gave a paper at Oxford University.

* * *

Dr. C. Walton Lillehei, University of Minnesota, is the 1958 recipient of the Oscar B. Hunter Memorial award of the American Therapeutic society, it was announced.

The award will be presented June 21 at the group's forty-ninth annual meeting in San Francisco. At the presentation, Lillehei will address the society on his work in "open heart" surgery to correct cardiac defects.

* * *

Dr. N. E. A. Leppo of Duluth turned over his practice to Drs. Ed Jorgenson and James Troutman, effective April 1.

* * *

An emotional outlet, as well as food, shelter and clothing, are needed in caring for the aged, **Dr. Robert J. Goldish**, Duluth, said in a talk to the thirty-seventh annual meeting of the Jewish Social Service Agency.

Families cannot adequately handle the needs of these people and the responsibility for caring for the aged must therefore become increasingly a community endeavor, he said. He spoke at a meeting in the Covenant Club.

* * *

Dr. Charles C. Cooper, Saint Paul, president of the Minnesota Academy of General Practice in 1953, has been elected vice president of the American Academy of General Practice.

* * *

Six Mayo Clinic staff men and members of the faculty of the Mayo Foundation participated in continuation courses in internal medicine and surgery at the University of Minnesota.

Dr. J. A. Bargen was on a panel discussing ulcerative colitis. **Dr. Charles H. Slocumb** discussed the current status of treatment of rheumatoid arthritis at the course on internal medicine.

At the surgery course, **Dr. Philip E. Bernatz** discussed treatment of breast cancer. **Dr. F. Henry Ellis** reviewed benign surgical lesions of the esophagus and also participated in a panel discussion. **Dr. Ward S. Fowler** described pulmonary function studies in relationship to resectability of lung and participated in another general discussion. **Dr. John M. Waugh** outlined treatment of diverticulitis and cancer of the pelvic colon.

* * *

Dr. Rodney F. Sturley, Assistant Professor, Department of Gynecology, University of Minnesota, was a recent speaker at a meeting of the Southwestern Minnesota Medical Society held in Worthington. "The Place of Cytology in the Diagnosis of Cancer" was the subject of Dr. Sturley's address.

(Continued on Page A-52)

You can specify PABLUM *with confidence*

Pablum Oatmeal is rich in Vitamin B that reduces irritability while furthering growth and repair. Natural vitamin and mineral content of oats is fortified in Pablum Oatmeal. Babies love the taste and smooth texture, too. For variety, baby can find his favorites among all five Pablum Cereals . . .

the baby cereals made to pharmaceutical standards of quality—especially processed for extra smoothness and lasting freshness.

PABLUM MIXED CEREAL • BARLEY CEREAL • RICE CEREAL • OATMEAL • HIGH PROTEIN CEREAL AND ASSORTED PAK

Pablum Products DIVISION OF MEAD JOHNSON & CO., EVANSVILLE, INDIANA • MANUFACTURERS OF NUTRITIONAL AND PHARMACEUTICAL PRODUCTS

(Continued from Page A-50)

Dr. Philip H. Utz, formerly of Rochester and now in private practice at LaCrescent, Minnesota, has joined the staff of St. Francis Hospital at LaCrosse.

* * *

April 27, 1958, was observed as Dr. Patterson's day in Fergus Falls. Residents of Ottertail County and the state joined with Fergus Falls in recognizing the contribution **Dr. W. L. Patterson,** superintendent of the Fergus Falls State Hospital has made to the mental health program of the state. Dr. Patterson has been a member of the hospital staff for forty-six years, serving as superintendent for the greater part of that time.

* * *

Two physicians who have been associated with the Olmsted Medical Group for the past year have elected as partners at the monthly meeting. They are **Dr. Malcolm K. Campbell** and **Dr. William R. Weyhrauch.**

* * *

Dr. Joseph Borg, Saint Paul, has been named to serve on a special advisory committee for Bethesda Hospital. The Committee of prominent Saint Paul men will supervise a drive for funds to finance a 100-bed hospital addition and a 142-bed infirmary across the street from Bethesda. A total of 750 volunteer solicitors participated.

* * *

Dr. Charles W. Mayo has been appointed chairman of a statewide Minnesota World Health Organization and Centennial Committee, it has been announced by Governor Orville Freeman, honorary chairman.

* * *

To express appreciation to **Dr. H. T. Petraborg** who has devoted the past twenty-three years to the people of his community, a project has been started by the Aitkin Community Hospital auxiliary to dedicate the nursery at the hospital in his honor. A nominal contribution of one dollar is being solicited from the 2,500 or more babies delivered by Dr. Petroborg since he started his practice in August, 1935.

* * *

Dr. Frank H. Krusen, head of the Section of Physical Medicine and Rehabilitation of the Mayo Clinic, Rochester, Minnesota, and professor of physical medicine and rehabilitation in the Mayo Foundation, Graduate School, University of Minnesota, has been appointed a member of the National Advisory Council on Vocational Rehabilitation by Secretary of Health, Education and Welfare Marion B. Folsom, Washington, D. C.

* * *

Recent Mayo Clinic Staff announcements include: **Dr. Richard W. Hill,** consultant in internal medicine; **Dr. Robert L. Sommerville,** consultant in medicine; **Dr. Anthony J. Bianco, Jr.,** consultant in orthopedic surgery; **Dr. Horace K. Ivy,** consultant in medicine.

* * *

Dr. Harry M. Weber, head of the Section of Diagnostic Roentgenology of the Mayo Clinic, Rochester, Minnesota, and professor of radiology in the Mayo Foundation, Graduate School, University of Minnesota, gave the

annual Fred Jenner Hodges lecture on radiology at the University of Michigan on April 11, 1958.

* * *

Dr. Frederick G. Gunlaugson, Minneapolis, has been named Hennepin County Tuberculosis Control Officer in action taken recently by the Hennepin County Sanatorium Commission. Dr. Gunlaugson currently is director of preventable diseases and tuberculosis control officer for the Minneapolis health department. If appointed to the county office, he would have jurisdiction over tuberculosis matters for the county as well as Minneapolis.

* * *

Dr. William A. O'Brien, Minneapolis, was a guest speaker at the March meeting of the McLeod County Medical Society at Glencoe. His subject was "The Use of Isotopes in the Diagnosis of Thyroid Disease."

Four independent physicians in Hutchinson joined together in group practice as of January 1 and moved into their new quarters, known as the Hutchinson Medical Center, on January 25. Physicians are—**C. O. Bretzke, Kenneth Peterson, George Smith,** of Hutchinson, and **Dan Huebert,** who returned to Hutchinson after completing his general surgical residency at St. Barnabas Hospital in Minneapolis.

* * *

Dr. William S. Eisenstadt, of Minneapolis, spoke before the Blue Earth Valley Medical Society at Fairmont, March 20, on the subject, "The Management of Bronchial Asthma, including Status Asthmaticus."

Doctor Gordon R. Kamman, Saint Paul, and Mr. Charles Murnane, Saint Paul attorney, addressed a joint meeting of physicians and lawyers at Morris, Minnesota, Monday, April 21, 1958. Sixty physicians and lawyers attended from ten surrounding counties. Their topic was "Medico-Legal Problems."

* * *

Only fifteen (0.3 per cent) of 5000 cancers seen in the head and neck service of Memorial Hospital, New York City, were malignant branchiomas. Of these, thirteen men and two women were over fifty years of age. In all these patients, the tumor appeared at about the level of the hyoid bone, the site of the highest nodes in the internal jugular chain, which is also the site in which cervical metastases from a primary in the oral cavity or pharynx are most likely to be found.

Communication

"McCARTHYISM"

Dear Editor:

I resent the use of editorial pages of MINNESOTA MEDICINE to defend recent controversial Supreme Court decisions. I am sure you know it is the opinion of many good legal minds and conservatives in general that the "Warren Court" has run rough shod over judicial precedents, taken to making political decisions, and violated the constitution in case after case.

Doctors have a right to question the motive of anyone using our editorial pages in this manner. However, to quote from a left-wing periodical from socialist England to influence our thinking is absolutely reprehensible. This was done in the January, 1958, MINNESOTA MEDICINE under the heading, "The Supreme Court Blow to McCarthyism."

To print something written by someone far removed from the scene, and take no responsibility for the same, is a technique very effectively used by pseudo-liberals as they push us down the road to socialism and the slave state. Please name the person (or persons) on the editorial staff who put this in the journal in order that he may be confronted.

I shall expect an early reply.

Very truly yours,
J. R. NICKERSON, M.D.

Fairmont, Minnesota
March 12, 1958

EDITOR'S NOTE: Doctor Nickerson, your unrepressed anger concerning the editorial on "McCarthyism" is undoubtedly shared by other true, red-blooded Americans of pure, stainless steel quality. You undoubtedly are a man of action and not one to sit back and simply criticize what others do. This is a great opportunity for you to write one or more editorials covering the subjects of "McCarthyism as Viewed by a Conservative," "The Warren Court," "Down the Road to the Slave State," "Our Pseudo-Liberal Editorial Staff" or any other political subject which may come to mind.

The editorials in MINNESOTA MEDICINE generally have educational value but are frequently dull and nonstimulating. A contribution from you might start a trend among Minnesota physicians to use their journal to express pent-up feelings on a variety of subjects. Simple "Letters to the Editor" will suffice, but a more polished "Editorial" will be more effective. Incidentally, I shall take no responsibility for the opinions expressed in your editorials and they must be signed by you.

Book Reviews

Books listed here become the property of the Ramsey, Hennepin and St. Louis County Medical Libraries when reviewed. Members, however, are urged to write reviews of any or every recent book which may be of interest to physicians.

BOOKS RECEIVED FOR REVIEW

ULCERATIVE COLITIS. Harry E. Bacon, B.S., M.D., ScD., LL.D., F.A.C.S., F.A.P.S. Professor and Head of Department of Proctology, Temple University Medical Center, Philadelphia; President, American Board of Proctology; Diplomate, American Board of Surgery and American Board of Proctology; Honorary Fellow, Royal Society of Medicine, Philippine College of Surgeons, Brazilian College of Surgeons, Japanese College of Surgeons. Foreword by Alton Ochsner, B.A., M.D., Sc.D., F.A.C.S., F.A.P.S. 395 pages. Illus. Price $15.00, cloth. Philadelphia: J. B. Lippincott Co., 1958.

ANTIBIOTICS ANNUAL, 1957, 1958. Edited by Henry Welch, Ph.D., and Felix Marti-Ibanez, M.D. 1070 pages. Illus. Price $12.00, cloth. New York: Medical Encyclopedia, Inc., 1958.

DIABETES AS A WAY OF LIFE. T. S. Danowski, M.D. Renziehausen Professor of Research Medicine, University of Pittsburgh School of Medicine; Senior Staff Physician at Presbyterian Woman's, Children's, Elizabeth Steel Magee, and Shadyside Hospitals of Pittsburgh; Consultant in Metabolism, Oakland Veteran's Administration Hospital, Pittsburgh. 177 pages. Illus. Price $3.50, cloth. New York: Coward-McCann, Inc., 1957.

OPERATIVE OBSTETRICS. By R. Gordon Douglas, Professor of Obstetrics and Gynecology, Cornell University Medical College, and William B. Stromme, Attending Obstetrician and Gynecologist, Northwestern Hospital and Fairview Hospital, Minneapolis. Foreword by Nicholson J. Eastman. 735 pages. Illus. Price $20.00. New York: Appleton-Century-Crofts, Inc., 1957.

Operative Obstetrics is a welcome addition to obstetrical literature and this volume should be useful to any practitioner specialist and student interested in this specialty.

The authors have organized their material to include all aspects of the practice of obstetrics, and each chapter contains basic practical information. A large number of photographs and diagrams demonstrate the techniques which the authors describe.

In the future, I hope the authors will revise the book as the need arises to keep abreast of modern trends so that this text can be perpetually used as a handy reference for physicians. It should be readily available in the hospital library.

JOSEPH F. MELANCON, M.D.

WOMAN'S AUXILIARY

HEALTH CAREERS FILM PREVIEW

(Continued from Page A-49)

ing of this film during the annual meeting in San Francisco, Wednesday, June 25, 3:00 P.M., Gold Room, Fairmont Hotel.

The film will be available to state and county medical societies for non-theatrical showings July 1, 1958.

AMA AUXILIARY PLANS JUNE CONVENTION

The call of the West will be heeded by physicians' wives as they travel to San Francisco in June for the thirty-fifth annual convention of the Woman's Auxiliary to the American Medical Association at the Fairmont Hotel. National committee meetings and round-table discussions will be held June 21-23 with formal opening of the convention slated for Tuesday morning, June 24. An interesting and varied program is being arranged by co-chairmen Mrs. Matthew N. Hosmer, San Rafael, and Mrs. Samuel R. Sherman, San Francisco.

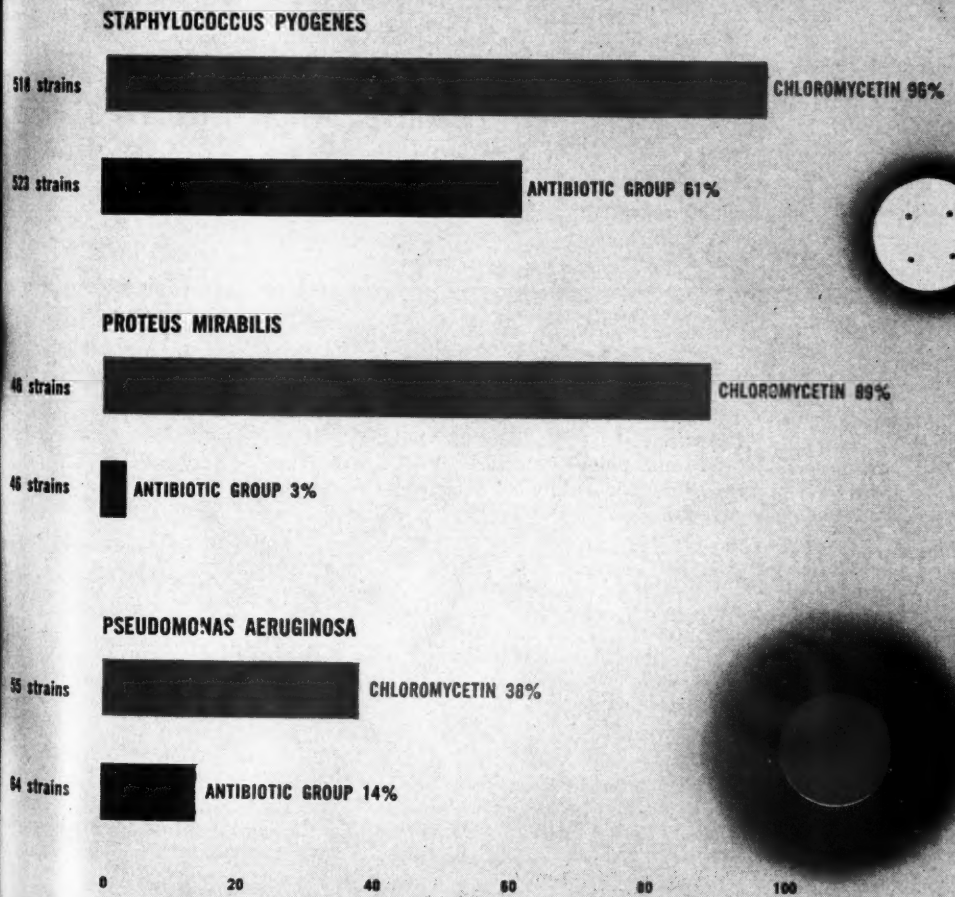
Business sessions on Tuesday and Wednesday will be devoted to state and national committee reports and discussions on current projects. Tuesday's luncheon in honor of past presidents will feature guest speaker, Mr. Richard H. McFeeley, principal of George School, Bucks county, Pennsylvania. Speaker at Wednesday's luncheon in honor of the president (Mrs. Paul C. Craig of Pennsylvania) and the president-elect (Mrs. E. Arthur Underwood of Washington) will be Dr. David B. Allman, immediate past president of the AMA. At this session, Mrs. Craig will present the Woman's Auxiliary contribution to the American Medical Education Foundation, and Dr. George F. Lull, AMEF president, will present AMEF awards to the auxiliaries.

Election and installation of national officers will be held Thursday morning with adjournment scheduled for noon.

ORGANISMS

ETIN®

IN VITRO SENSITIVITY OF THREE COMMON PATHOGENS TO CHLOROMYCETIN AND TO A WIDELY USED ANTIBIOTIC GROUP*



*Adapted from Roy, T. E.; Collins, A. M.; Craig, G., & Duncan, I. B. R.: *Canad. M.A.J.* 77:844 (Nov. 1) 1957.